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PEMPHIGUS AND PEMPHIGOID.

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THE validity of histological criteria for the definition of pemphigus has become widely recognized since the important work of Civatte (1943) and of Dupont and Pierard (1938). There are, however, still many dermatologists who find difficulty in accepting as distinct from pemphigus those pemphigoid eruptions which sometimes closely resemble it clinically and bear little resemblance to classical Duhring's dermatitis herpetiformis. We believe that these pemphigoid eruptions are a manifestation of a pathological process fundamentally different from that of pemphigus. The French classify them with dermatitis herpetiformis (*dermatites polymorphes*), with which they share a common histology, but they differ so widely from Duhring's dermatitis herpetiformis in their natural history that there are grounds for keeping them as a distinct group, and to avoid confusion we propose to refer to them as Pemphigoid. The term "bullous pemphigoid" was recently adopted by Lever (1953) and is perhaps preferable to "senile dermatitis herpetiformis" which we have previously employed, and to "benign chronic pemphigus" which Lever favoured in his earlier articles. It is, however, clumsy and repetitious. The general acceptance of such terms as "typhoid" and "erysipeloid" offer obvious precedents for the term we are employing, which was suggested by Church (1953).

This paper is based on a study of 54 bullous eruptions, of which 38 were pemphigoid and 16 pemphigus. Our object has been to compare the clinical features, course and response to treatment of these two groups, classified according to their pathology. We have accepted as pemphigus those cases in which the bullae were apparently formed within the epidermis by acantholysis.

The remaining cases with bullae beneath an intact epidermis were classified as pemphigoid. We have not included any patients we have followed for less than a year.

Age and Sex Incidence.

Pemphigus :

Age at onset.	Male.	Female.	Total.
20–29	1	0	1
30–39	0	1	1
40–49	1	0	1
50–59	4	0	4
60–69	5	3	8
70–79	1	0	1
Total	12	4	16

Pemphigoid :

Age at onset.	Male.	Female.	Total.
20–29	1	0	1
30–39	0	0	0
40–49	0	0	0
50–59	0	4	4
60–69	6	7	13
70–79	8	9	17
80 plus	2	1	3
Total	17	21	38

The number of cases is too small for any statistically valid conclusions, but it is interesting that only one of our 16 cases of pemphigus, but over half of the pemphigoid subjects, were over 70.

Mode of Onset.

Pemphigus.—Our series includes three examples of the Senear-Usher syndrome. On account of the special features of this phase of pemphigus we are excluding these cases from this part of our study. In 10 of the remaining 13 cases the site of the initial lesions was recorded :

Mouth only	2
Mouth and vulva	1
Mouth and scalp	2
Scalp only	1
Trunk	2
Legs	2

In most patients the initial lesions were moist crusts but occasionally large bullae. Where the mouth was involved the lesions were described as ulcers or as stomatitis. In all patients the eruption eventually became widespread. The interval which elapsed between the appearance of the initial lesion and generalization of the eruption was never less than two weeks nor more than six months and in most patients was about three months. The buccal mucous membranes were eventually involved in 12 of the 13 patients (92%). In two patients there were conjunctival lesions and in one urethritis.

Pemphigoid.—In the pemphigoid eruptions the lesions were also localized for a variable period after their onset. Whereas in pemphigus the initial lesions were often confined to a small area the localization of pemphigoid lesions was less marked, but characteristically the eruption of large tense bullae was for a time confined to one region of the body. The initial lesions were large bullae in all except 4 cases. Although the bullae were usually clear, in several patients they were haemorrhagic—a feature we have not observed in pemphigus. In three patients urticarial wheals, often gyrate, were present together with the bullae. In one patient the bullae were flaccid and crusting. The interval before generalization of the eruption was usually between 2 and 3 months, but in one patient was a year. The site of the initial lesions was recorded in 32 cases :

Legs or feet	13
Arms	8
Arms and legs simultaneously	4
Trunk	2
Head or neck	4
Buccal mucosa and conjunctiva	1

The buccal mucosa was ultimately involved in 5 patients (13·5%). The conjunctiva was involved at the same stage in two patients; both were men, aged 23 and 60, and the clinical picture was ultimately that of ocular pemphigus.

Course.

Pemphigus—If the 3 cases of Senear-Usher type are again excluded the remaining 13 cases were all fatal after an average duration of $8\frac{1}{2}$ months. The longest survival period was 26 months and only 3 patients lived more than a year.

Duration of 13 *Fatal Cases.*

2 months	2
3 ,,	3
4 ,,	1
5 ,,	1
9 ,,	1
1 year	2
$1\frac{1}{2}$,,	2
2 ,,	1

Pemphigoid.—Twelve of 38 patients have died after an average duration of 14·5 months. Five patients lived over a year and one for 4½ years. The shortest survival was 6 months.

Duration of 12 Fatal Cases.

6 months	3
7 „	1
8 „	1
9 „	2
1 year 1 month	1
1 „ 3 months	1
1 „ 8 „	1
2 years	1
4½ „	1

The 26 surviving patients with pemphigoid eruptions have all been followed for at least a year after the onset of the condition. The course of the eruption was exceedingly variable, in contrast with the much more uniform evolution of our cases of pemphigus. In two patients the bullae remained localized throughout the course of the eruption to the sites initially involved. In one patient the eruption was localized to the legs for two weeks, then spread to the thighs and arms, clearing after three weeks on sulphapyridine, but recurring only in the original sites six months later.

Such localized or partially localized eruptions are exceptional, and in 26 of our patients the eruption became generalized and involved the greater part of the body.

Since all the patients in this series have received treatment of some kind our figures may not give a true indication of the natural history of the condition.

With treatment the patients fall roughly into five groups :

a. Eight patients had single attacks of 3 weeks' to 5½ years' duration, followed by complete remissions, and have remained free of symptoms without further treatment for from 1 to 5 years.

b. Eight patients have had no significant remission since the onset of the disease. The longest duration without remission was 33 months. Five of the fatal cases are in this group and died after 6 to 15 months.

c. Seven patients have had recurrent attacks alternating with complete remissions—two to four attacks of 3 weeks' to 9 months' duration (average 3 months) at intervals of 4 weeks to 1 year.

d. Five patients have had no complete remission, but have had variable periods of relative freedom from the eruption even without treatment.

e. Six patients could be maintained in remission or in partial remission only while receiving treatment, but relapsed when treatment was discontinued.

Response to Treatment.

Pemphigus.—We have seen no definite evidence of the beneficial effect of any treatment on pemphigus. None of the remissions attributed to treatment has been outside the scope of natural remissions. ACTH and cortisone were not available at the time these patients were under treatment.

Pemphigoid.—Most patients received more than one form of treatment and there was wide variation in response. Some patients were completely controlled by one drug and uninfluenced by others. Some were completely or partially controlled by any one of three or more drugs. A few were totally uninfluenced by any form of treatment. Arsenic proved the most generally useful drug and was given in the form of Fowler's solution to twenty patients. Nine were completely or almost completely controlled and a further 7 or 8 were significantly improved. Of 17 patients receiving sulphapyridine 4 were controlled, 7 were stated to be improved, 4 uninfluenced and 2 aggravated. Stovarsol was given in 3 cases and Suramin in 2, with significant improvement. Six patients were apparently uninfluenced by any form of treatment.

Cause of Death.

Too few of our cases were submitted to autopsy to enable us to make any positive contribution on this question. It is, however, our impression, confirmed by conversation with other dermatologists, that pemphigoid is not in itself a fatal disease. In patients dying of pemphigus there may be no other discoverable cause of death : in pemphigoid death usually results either from complications such as broncho-pneumonia or from progressive diseases already present before the development of the eruption. We have already drawn attention to the fact that pemphigoid afflicts mainly the very old ; a majority of its victims are also in poor general health. In many such cases pemphigoid is apparently mainly a contributory factor and not the principal cause of death.

The possibility that there is a causal relationship between cancer and pemphigoid or dermatitis herpetiformis has occasionally been suggested (Bogrow, 1909 ; Elliott, 1938 ; Tobias, 1951 ; Epstein, 1952). Three of our patients with pemphigoid were found at autopsy to have had carcinomata (bronchus, cervix uteri, colon). Since pemphigoid and cancer have much the same age incidence no causal relationship can be claimed on the present evidence, but further investigation is obviously called for.

Pemphigus Erythematosus (Senear-Usher).

We believe that pemphigus vulgaris, foliaceus, vegetans and erythematosus are manifestations of the same basic pathological process ; they show essentially the same histological changes with certain minor modifications. Cases of pemphigus erythematosus have been excluded from our figures on account

of their special clinical features and usually more benign course, and because clinically the differentiation of these cases from the pemphigoid eruption is unlikely to present any difficulty.

One of our cases of Senear-Usher type, a woman aged 60, had had crusted seborrhoeic lesions of the back for six years. She is alive and well and has improved after each of four courses of Suramin. The second case, a man aged 46, had for many months only the Senear-Usher type of crusted lesions of the chest and back, but he later developed widespread bullae. He subsequently reverted to the Senear-Usher form and remains alive and well after three years. The third patient, a man aged 69, had Senear-Usher type of lesions of the chest and back. Shortly before his death, eight months after the onset of the condition, he developed a generalized bullous eruption.

These three cases illustrate both the connection between pemphigus erythematosus and pemphigus vulgaris and the relatively benign course which the former variety may pursue in some cases. Pemphigus erythematosus may perhaps be considered a phase of pemphigus in which the basic disease process of pemphigus, whatever that may prove to be, is in a state of temporarily reduced activity. While this phase persists the prognosis is relatively good but the duration of the phase is unpredictable in any given case.

Conclusions.

Analysis of our cases has defined a clinical picture of a bullous eruption differing in many ways from classical Duhring's dermatitis herpetiformis, although sharing with it a histology quite unlike that of pemphigus. This eruption may at times clinically resemble pemphigus vulgaris quite closely, but the diagnosis can often be suspected on clinical grounds. The main differences between the two eruptions can be summarized as follows :

	Pemphigus vulgaris.	*Pemphigoid.*
Sex incidence	Males three times as often as females	Males and females equal.
Age of onset	76% between 50–70, 6% over 70	53% over 70.
Most common site of initial lesion	Scalp, mucous membranes	In order of frequency—legs, arms, head and trunk.
Commonest initial lesions	Localized crusting or mucosal ulceration	Groups of tense bullae sometimes haemorrhagic; occasionally red urticarial plaques.
Mucosal involvement	Common and early	Rare and late.
Prognosis	Uniformly bad	Bad only in old people and in those with extensive mucosal involvement.
Treatment	None effective	Sometimes controlled by arsenic or sulphapyridine.
Course of the disease	Steady evolution and deterioration	Varied course, often recurrent attacks and spontaneous remissions lasting months to years. Sometimes single attacks of short duration.

In general our conclusions are in agreement with those of Lever (1953). However, in the majority of our cases of pemphigoid the lesions were localized

to one region for about three months before the eruption generalized, whereas in Lever's cases the eruption was widespread from the beginning.

It seems probable that pemphigus in its various forms will ultimately be proved to be a morbid entity. Pemphigoid is probably a syndrome with more than one cause.

Summary.

A clinical study of 54 bullous eruptions classified as pemphigus or pemphigoid according to histological criteria.

Pemphigoid is shown to differ from pemphigus in its clinical features, course, prognosis and response to treatment.

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A PRELIMINARY ELECTRON MICROSCOPE STUDY OF DERMATITIS HERPETIFORMIS AND PEMPHIGUS VULGARIS.

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As part of a recent follow-up study of cases of dermatitis herpetiformis attending the General Infirmary at Leeds, it was decided to take advantage of the more detailed histological information afforded by the electron microscope. An examination of a typical lesion in one case of dermatitis herpetiformis revealed abnormal collagen fibrils in the dermis: many misshapen fibrils with frayed ends and much amorphous material were observed. For comparison a typical lesion from a case of pemphigus vulgaris was similarly examined and no abnormalities were noticed, the dermal collagen fibrils being indistinguishable from those of normal skin. In view of these findings, six patients with dermatitis herpetiformis and four patients with pemphigus vulgaris were further investigated. In the pemphigus group three patients, all of whom have since died, showed the malignant type, and one case was of the relatively benign Senear-Usher type.

Three of the patients in the dermatitis herpetiformis group (Cases 2, 4 and 6) might, owing to the age of onset, be classified by some as senile dermatitis herpetiformis or "bullous pemphigoid." But in view of our findings, i.e., the absence of collagen changes in cases of pemphigus vulgaris, compared with collagen changes found in all those cases excluded from the pemphigus vulgaris group, it is proposed in this preliminary communication to retain these three cases under the one heading of dermatitis herpetiformis, although it is realized that dermatitis herpetiformis and "bullous pemphigoid" eruption might be separate clinical entities in themselves.

The material examined with the electron microscope was taken by means of a biopsy punch from the floor of a bulla or vesicle, and for comparison from an area of unaffected skin. Material was also taken from the raised infiltrated erythematous areas found in all the cases of dermatitis herpetiformis. In each the fluid from the bulla or vesicle was drawn off, and stored in sterile tubes so that examination for virus bodies could be made.

Histological examinations of bullous or vesicular lesions were carried out in six of the cases (dermatitis herpetiformis, three cases; pemphigus vulgaris of the malignant type, three cases). As it was impossible to obtain material

from the same lesion sufficient for both investigations, the histological material was taken from similar lesions in the same patient.

The results are shown in Table I and typical electron microphotographs are shown in Figs. 2, 3 and 4.

Case.	Age.	Sex.	Disease.	Duration.	Electron miscoscopy examination.	Histological examination.
1	50	M.	Dermatitis herpetiformis	2 years	Slightly more amorphous material than in normal skin. A few degenerate collagen fibrils seen, i.e., shortened and with frayed ends, the majority of the fibrils being clearly outlined and apparently undamaged	Subepidermal vesicle.
2	63	F.	Ditto	3 „	An excess of amorphous material with many degenerate collagen fibrils. Some coated with the amorphous material	Not examined
3	39	M.	„	25 „	Degenerate collagen fibrils, many coated with an amorphous material	„
4	72	M.	„	2 months	Gross excess of amorphous material, tending to obscure most of the collagen. Degenerate collagen fibrils	„
5	37	M.	„	7 years	Gross excess of amorphous material, tending to obscure most of the collagen. Degenerate collagen fibrils	Subepidermal vesicle
6	67	F.	„	6 months	An excess of amorphous material covering many collagen fibrils ; many of these were degenerate	Ditto
7	67	F.	Pemphigus vulgaris	3 years	No degenerate fibrils. Collagen clean and well defined. Normal amount of amorphous material	Not examined
8	48	F.	Ditto	2 „	No degenerate fibrils. Collagen quite clean and well defined. Normal amount of amorphous material	Intra-epidermal vesicle
9	56	F.	„	5 months	Unaffected skin normal. The floor of the bulla showed no excess of amorphous material but slight degeneration of the collagen with kinking and fraying of the ends	Ditto
10	73	M.	„	7 „	No degenerate fibrils. Collagen quite clean and well defined. Normal amount of amorphous material	Subepidermal vesicle

Case 7 : This was a typical case of pemphigus vulgaris of the Senear-Usher type. The disease is still active after five years.

Cases 8 and 9 : These patients were clinically typical of pemphigus vulgaris, and have since died, within two years of the onset of the disease.

Case 10 : This patient, in spite of the histological subepidermal vesicle found in one bulla on one occasion, was still considered to be a typical case of pemphigus vulgaris, and has since died from the disease 18 months after the onset.

In Cases 1 to 6 the material examined was from the floor of a vesicle, from a raised infiltrated erythematous area, and from an area of unaffected skin.

In Cases 7, 8 and 10 the material examined was from the floor of a bulla, and from an area of unaffected skin.

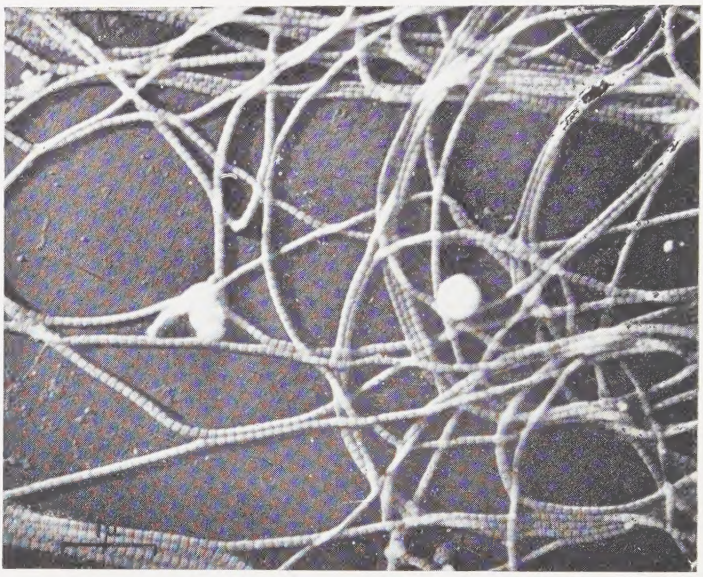

FIG. 1.—Dermal collagen from normal skin. Note the typical cross-striated appearance, the relative straightness of the fibrils and the absence of frayed ends. A slight amount of amorphous material is present. × 12,500.

FIG. 2.—Dermal collagen from clinically normal skin (dermatitis herpetiformis) showing shortened fibrils, some with frayed ends. Much amorphous material is also present. × 14,000.

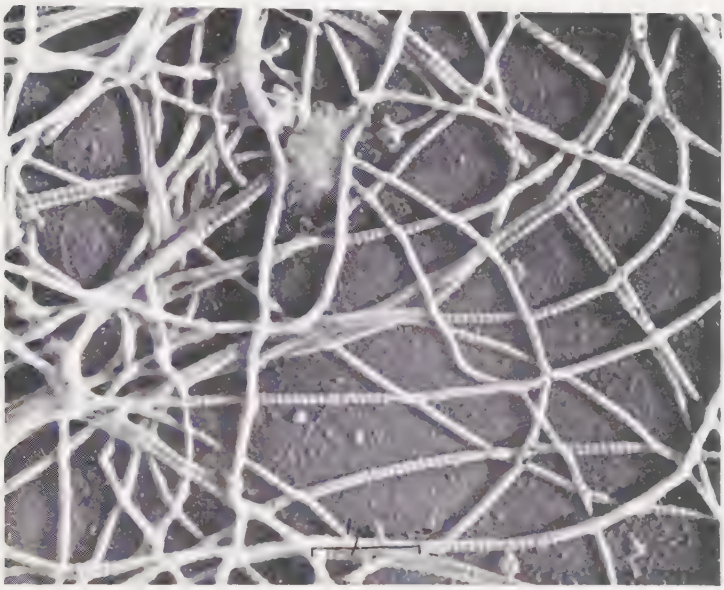

FIG. 3.—Dermal collagen from base of bulla (pemphigus vulgaris) showing clean and apparently normal fibrils. × 14,000.

FIG. 4.—Dermal collagen from base of bulla (pemphigus vulgaris), Case 9 showing some shortened fibrils with frayed ends. A slight amount of amorphous material is also present. × 14,000.

Discussion.

All the cases of dermatitis herpetiformis showed changes in the collagen, i.e., misshapen and shortened fibrils, with an excess of dermal material in every phase of the lesion (Fig. 2). Similar changes were seen in the apparently unaffected skin. In contrast, three out of the four cases of pemphigus showed no such changes in the floor of the bulla or in the unaffected skin, the appearance of the dermis being indistinguishable from normal (Figs. 1 and 3). The remaining case (Case 9) showed slight abnormal collagen changes in the base of a bulla (Fig. 4), while an unaffected area of the skin appeared normal.

Since similar changes in the dermis were found both in the unaffected skin and in all phases of the lesions in the cases of dermatitis herpetiformis, it seems that the initial process in this disease probably arises in the dermis. This is in keeping with the subepidermal position of the vesicle found on histological examination.

In pemphigus vulgaris on the other hand no abnormal changes were found in the dermis, except beneath a bulla in one case. This is consistent with the usual histological finding in which the lesions appear initially in the epidermis.

In two cases of pemphigus vulgaris which were clinically typical in all respects there was some evidence of changes in the dermis. Case 9 showed on electron microscope examination abnormal collagen changes in the floor of a bulla, although the histological examination of another lesion revealed an intraepidermal vesicle. In Case 10, histological examination of a typical lesion showed a subepidermal vesicle, although the electron microscope examination of another lesion showed no change in the collagen. These findings suggest that in some lesions of pemphigus the initial process may extend into the dermis, or may relate to the occasional difficulty in diagnosis.

The vesicle fluids examined in every case gave no indication of virus bodies It is unlikely therefore that these two diseases are caused by viruses.

These preliminary findings do not conflict with the view that the primary lesion in dermatitis herpetiformis is subepidermal, while the early lesion of pemphigus vulgaris is intraepidermal. In some cases the lesions of pemphigus may extend into the dermis to produce changes in the collagen structure. Further, electron microscopical changes in dermatitis herpetiformis appear to involve all areas of the skin irrespective of any clinical change. It appears therefore that electron microscope examination may be useful in distinguishing between the two diseases by means of (i) the collagen changes in dermatitis herpetiformis compared with the normal appearance in pemphigus vulgaris, and (ii) the collagen changes in the clinically normal skin in dermatitis herpetiformis.

The electron micrographs were obtained by the kind permission of Professor W. T. Astbury, Department of Biomolecular Structure, University of Leeds. We wish to thank Dr. J. T. Ingram and Dr. F. F. Hellier for allowing us access to these cases.

THE DERMAL MELANOBLAST: SOME CYTOLOGICAL AND SPECTROPHOTOMETRIC FEATURES.

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A. Cytology.

In 1904 Münch noted four features of the uveal chromatophores: they formed a syncytial network; the cytoplasm contained numerous fibrils lying in the long axis of the cell and in a zigzag or spiral pattern across its breadth; the melanin granules, if fine, were arranged in accordance with the fibril pattern: coarse granules were apt to obscure the pattern of the fibril system.

Münch's observations were substantiated in the present study, although the investigation was carried out on dermal melanoblasts and not uveal "chromatophores." There is, as Bloch (1927) pointed out, no actual difference between these two cell types.

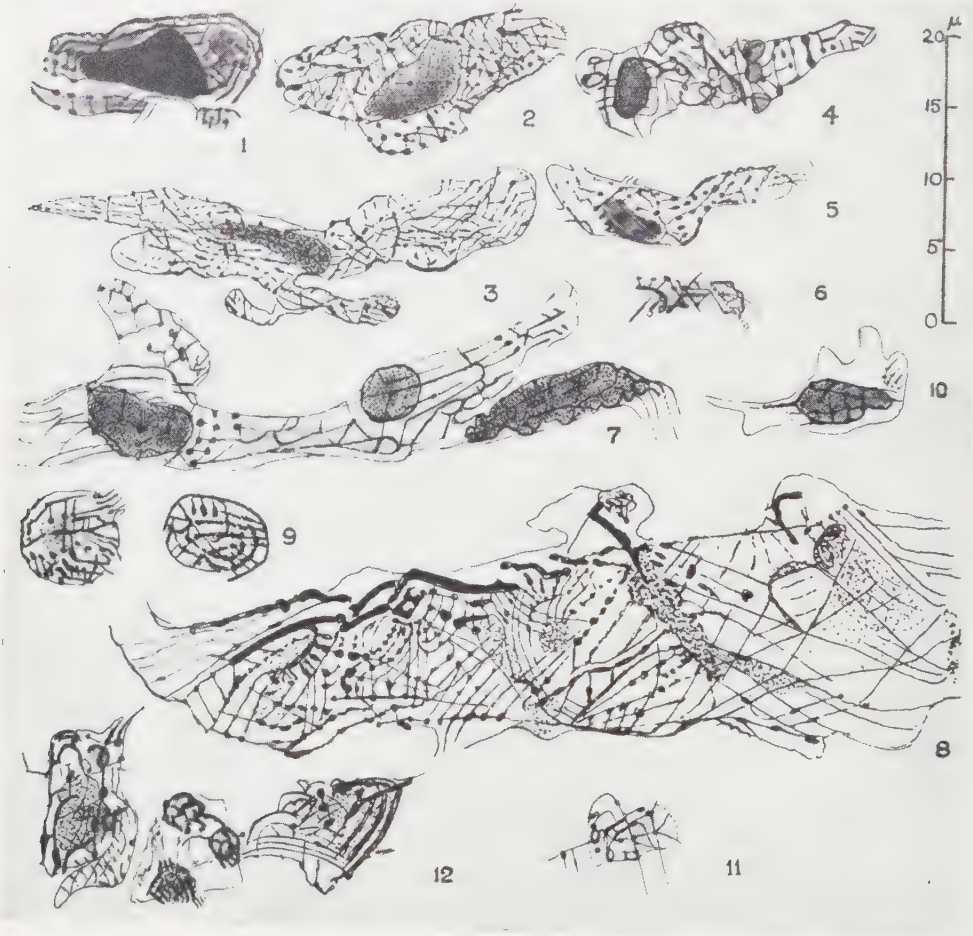
Since these cytological features are not generally known, an attempt was made to work them out more fully and to see what conclusions might be reached. For this purpose, dermal melanoblasts were studied both in histological sections and in smear preparations of fresh material from several specimens of dermal melanoses, blue naevi and melanosarcomas in man and animals.

Cytoplasmic Fibrils.

Since the cytoplasmic fibrils of dermal melanoblasts are intimately related to cell melanization I propose to call them *melanoglia* fibrils, in accordance with the terminology proposed by Mallory (1904) for similar fibrils. For convenience one may recognize two different thicknesses of fibril, a thin and a thick (Fig. 1), but the thin ones predominate and transitions between the two extremes are frequent. Attached to the fibrils are small refractile particles, which appear to represent the unmelanized framework of melanin granules.

Thin melanoglia fibrils lie near the lower limit of microscopic visibility. Owing to their thinness it is difficult to ascribe a colour to them. They are easily obscured in areas where the cytoplasm stains deeply. They usually lie about 1μ apart, and run in roughly parallel rows along both the length and breadth of the cell (Fig. 2). Two longitudinal fibril streams may sometimes be distinguished lying at different depths in the cytoplasm and differing slightly in direction (Fig. 3). In the dendritic processes the fibrils running across the width of the process may often suggest the cross-striations of muscle

(Figs. 1, 3, 4). In broader parts of the cell these fibrils are not transverse but often somewhat oblique (Fig. 5). Two such oblique layers are often seen at different depths in the cell, each layer showing a uniform degree of slant of the fibrils, but the direction of the slant is reversed in the second layer (Figs. 2, 3). This appearance led Münch to suppose that the fibrils running across the cell



Figs. 1–12.—Camera lucida drawings of melanoblasts and parts of melanoblasts in sections and smears to show the types and patterns of the cytoplasmic fibrils and the relation of melanin granules to them. Details in text.

formed a spiral. He considered that one was actually focussing on the nearer and farther turns of a continuous coil. This seems to have been an oversimplification, although a proper three-dimensional pattern of the fibril system can still not be offered. Some complexities of the thin melanoglia pattern will now be mentioned.

The direction of the fibrils is modified by the dentrites, into each of which a bunch of fibrils is diverted from the main protoplasmic complex (Fig 3). Anastomoses between the oblique and longitudinal fibrils produces various patterns, most usually, as one focuses, a comb-like (Fig. 1) or a herring-bone like effect (Fig. 6). The longitudinal fibrils may also be connected by obliquely placed festoons of anastomotic fibrils (Fig. 7). In Giemsa-stained smears of blue naevus cells the oblique fibrils do not form a spiral, but converge fanwise on definite loci (Fig. 8). When one sees a cell body in transverse section (Fig. 9), a slanting oblique fibril tends to form an angular vortex with streams of anastomotic fibrils arising from it. In favourable places the fibril stream can be traced from one nuclear region to another in the melanoblast syncytium (Fig. 7).

In the ground substance around the melanoblasts one can sometimes see a faint, practically colourless fibrillar pattern which corresponds in direction to that of the melanoglia. Nerve fibres approach the melanoblasts in the same direction as these fibrils in the ground substance. This correspondence in direction of ground substance fibrillation, nerve fibre courses and melanoglia patterns may lead one to regard the extracellular extension of the melanoglia pattern as a periterminal nerve network, or else to suppose a direct anastomosis probable between nerve and melanoglia. However, it was not clear what the extracellular extension of the melanoglia pattern might be, nor was any true link established between nerve fibres and melanoglia fibrils.

Thick melanoglia fibrils appear to arise by a swelling of the thin fibrils. This swelling varies in degree and extent, being sometimes focal and nodular, producing an irregular border to the fibril, and at other times diffuse, making the fibril look like a minature fungal hypha (Figs. 1, 8, 12). Thick fibrils may show tiny foci of greater translucency along their course. Thick melanoglia does not show the same sharp angular anastomoses seen among thin fibrils. The fibrils appear less pliable, and Y-shaped branches are commoner than the T-shaped junctions of thin melanoglia. Thickening of melanoglia commonly affects the longitudinal fibrils at the surfaces of the dendritic processes and in the perinuclear area. Nuclei so surrounded may look corseted (Fig. 10). A leash of thick melanoglia, when melanized, can look like a large dense melanin granule (Fig. 12).

The fibrils can be seen best in Giemsa-stained sections and smears. Unstained, or with the haematoxylin-eosin and periodic acid-Schiff techniques they could also be studied, although they did not take up the stain from the Schiff reagent. Mallory's phosphotungstic acid-haematoxylin, Gram and methyl green-pyronin techniques were less satisfactory. Disappearance of the fibril pattern after bleaching was noted by Lauber (1936). Silver techniques obscured the pattern almost entirely.

Melanization.

Several sorts of melanin deposit can be distinguished in the melanoblast. The following structures show the presence of pigment, which varies both in density and colour: the cytoplasm, the melanoglia, the nuclear membrane and small and large granules.

The *cytoplasm* of the dermal melanoblast is usually a diffuse light brown colour in haematoxylin and eosin preparations, with occasional areas of brilliant pink and also pale blue-green near the nucleus. I am assuming that the brown substance, and perhaps also the pink and the blue-green, is melanin. Melanization of the *melanoglia fibrils*, especially the thick ones, and of the nuclear membrane may also take place. From examination of smears the melanin appears to be precipitated as a black pigment on the surface of these structures, recognizable as a coating because of its patchiness and density at the surface of structures seen edgewise. When these fibrils and the nuclear surface are melanized in continuity, the apparent picture of nuclear budding with extrusion of intranuclear melanin may perhaps be produced (Meirowsky and Freeman, 1951). Thick melanoglia may break up into heavily melanized blocks of melanin; an appearance like hyphae with arthrospores is thus produced.

On the melanoglia, near or at the points of fibril intersection, there are to be found tiny refractile particles regularly attached by part of their surfaces to the fibrils (Figs. 6, 8, 11). It appears as if the typical *small melanin granules* of round or oval shape are formed by a melanization of these particles. Melanization seems to proceed over the particle from the points of fibril attachment, producing at first a polar melanization only, and later a complete blackening of the particle. Rows of granules on a fibril look like beaded threads in which each bead is elongated in the line of the fibril (Fig. 5). Although a cell may seem to be heavily melanized and full of granules, many fibrils show little melanization and have relatively few granules along them.

A *large melanin granule* results from the melanization of a larger glassy body of variable shape, often somewhat angular. These bodies also seem to be attached to fibrils. These fibrils appear black and the melanized bodies pale brown. This type of melanin granule is usually thought to be characteristic of chromatophores, but Fig. 4 shows these features in a melanoblast from a blue naevus.

Since a separation of the dermal melanoblast from the dermal chromatophore is made, amongst other things, on the type of granule, these larger granules were further investigated. Fig. 13*a* shows a row of six granules drawn freehand from cells which were typical dermal chromatophores. The section was from a case of incontinentia pigmenti in which dermal melanoblasts were absent. One notes that the granules are attached to fibrils which are also furnished with small melanin granules. Variable black melanization of the large body is noted, often along the course of the attached fibril, while

the rest of the body is pale brown. Fig. 13*b* shows a series of granules in melanoblasts from a human melanosarcoma of Darier type. The large granule may at first sight seem to consist of a grouping of the smaller granules—an agglutination of granules—but this is actually not the case. The small granules are still merely part of the fibril pattern in the vicinity of a large granule. Fig. 13*c* shows three granules from cells presumed to be chromatophores lying among dermal melanoblasts in an extrasacral Mongolian spot. In this instance it was impossible to say on morphological grounds whether the cells concerned were chromatophores or melanoblasts. Fig. 13*d* shows two granules from melanoblasts of an equine melanosarcoma. Again a fine melanoglia

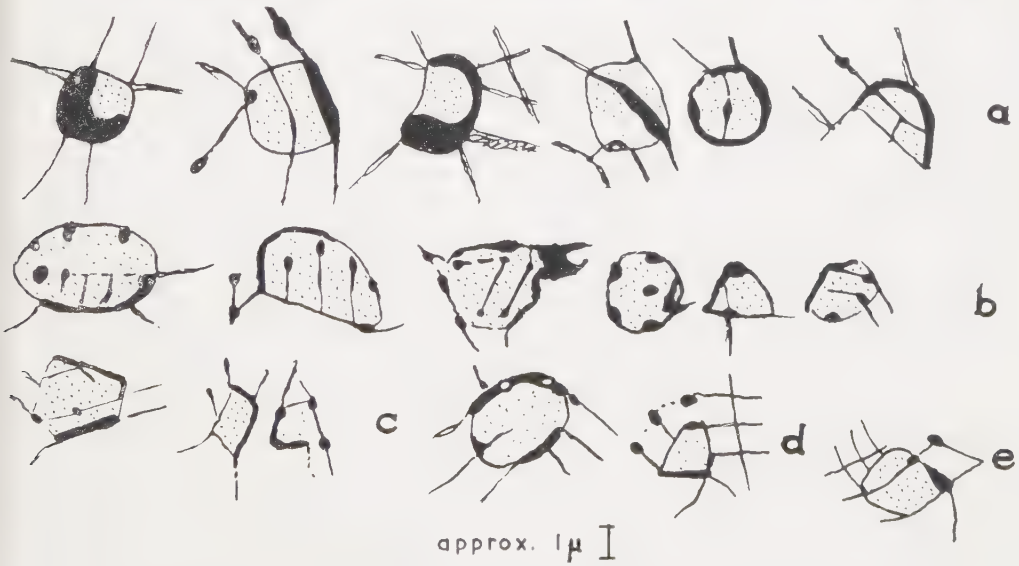


FIG. 13.—Freehand drawings of single melanin granules of the " chromatophore " type. Essential similarites, whether from melanoblasts or chromatophores. Sources in text.

pattern is present, to which a " chromatophore type " of melanin granule is attached. Fig. 13*e* illustrates another example of a " chromatophore type " of granule from a dermal melanoblast of *Cercopithecus*. One must therefore conclude that these structural details in chromatophores and melanoblasts have no decisive value in separating the cell types.

DISCUSSION.

The structure of the dermal melanoblast seems to permit some deductions on melanin migration. If melanin granules are attached to an apparently fixed fibrillar system in the melanoblast, it is difficult to believe in a free migration of granules within the cell or a ready liberation of granules from the cell. It seems that the fibril system would have to be disrupted before these

things could happen. There is no indication in the dermal melanoses examined that such a disruption occurs. It must at all events be rare.

Some theoretical deductions can be made from this assessment of the position. Firstly, the cells form a syncytium, and it seems more likely that the melanin granules could be formed by diffusion along the dendritic anastomoses of the non-granular cytoplasmic melanin. This could then be precipitated in granule form on the fibrils in the receptor cell. Secondly, it appears reasonable to suggest that the *fixed* dermal chromatophores are also part of the dermal melanoblast syncytium, despite being DOPA-negative, since their individuality in respect of granules, dendrites, melanoglia and situation of the skin is actually difficult to uphold. Without denying that histiocytes take up melanin, it could nevertheless be suggested that many dermal chromatophores are not histiocytes, but regionally differentiated neural cells (see below), acquiring and precipitating pigment by diffusion through the syncytium of soluble melanin and not by phagocytosis of particulate melanin.

The affinities of the dermal melanoblast must now be considered. They may be modified mesodermal cells, but they nevertheless do not resemble fibroblasts ; fibroglia fibrils differ considerably from melanoglia. On the other hand, they may have affinities with certain cells of the nervous system. Boeke (1940) has discussed the possibility that elements of the mesoderm may be functionally integrated into the construction of the nervous periphery. The dermal melanoblast may then represent such an element. The more specifically neural cells which are relevant to the problem are lemnoblasts, Schwann (or Remak) cells, Langerhans cells and interstitial (or intercalary) cells. The definition and character of these cells will not be dealt with here, since this has already been done by Leeuwe (1937), Boeke (1936, 1940), Masson (1947, 1950), De Castro (1951), Ferreira-Marques (1951), Feyrter (1951), and Wiedmann (1951, 1952). Among the possible " neural " cells the one which most closely resembles the dermal melanoblast is the corium type of Langerhans cell described by Wiedmann as a neurohormonal cell, and considered by him to be equivalent to the intercalary cell of Feyrter. The view that melanoblasts and Langerhans cells are morphologically related was first proposed by Leydig in 1876, and developed by him later in a series of publications (Münch, 1904). It may be a difficult relationship to defend if the epidermis alone is considered, but in the dermis the resemblances are striking. Professor Wiedmann tells me that he believes that the dermal interstitial cells (equivalent of the Langerhans cell) are capable of producing melanin. If the cells which he describes are really part of the nervous system his view seems correct, since he has noted cytological features in unmelanized nerve cells similar to those I have found in typical dermal melanoblasts. Ferreira-Marques, on the other hand, calls the corium equivalent of the epidermal Langerhans cell a Schwann cell. An affinity between dermal melanoblasts and Schwann cells seems somewhat

less certain, since the latter are not supposed to act as intrinsic transmitters of the nervous impulse. On the other hand, if it is accepted that the interstitial cells and Schwann cells are identical (De Castro, 1951) and that the interstitial cells are true ganglion cells (Leeuwe, 1938) there need be no further discussion.

If one must call the melanoblast a neural cell, it is necessary to decide whether the fibrils are neurofibrils or not. Boeke (1936) thought that they could not be neurofibrils, since the connection of the cells with actual nerve fibres was not frequent enough to suggest this functional relationship. Nevertheless, despite the peculiarities of the glia pattern, it seems reasonable to believe that the melanoblasts are "neural" cells, more probably of the vegetative nervous system because of their relationship to blood vessels as well as nerves, but the present study suggests no more exact cell affinities.

B. Spectrophotometry.

Several suggestions have been put forward to explain the blue colour frequently seen in dermal melanoses. Tièche (1906) said that the darkly coloured melanin did not differ from brown epidermal melanin, but appeared blue because it was deeply placed in the skin and was seen through the turbid overlying medium. Bloch (1927) stressed the importance of a band of subepidermal collagen above the pigment cells and the depth of the cells from the surface as the two factors causing the blue colour "*aus optischen Gründen.*" Imschenetzky (1930), a Russian author, stated that the blue colour comes about by an accumulation of a sufficiency of pigment—a splendid example of the change of quantity into quality. Edwards and Duntley (1939) implicated the Rayleigh scatter phenomenon in the production of the blue colour. They considered that a blue scatter from the turbid epidermis became manifest when backed by an absorbent layer of pigment in the corium. Meanwhile, they paid no attention to the optical properties of the corium itself. In a previous paper (Findlay, 1951) I considered that all these views must be wrong, because the pigment layer was still blue when the overlying strata were dissected away. These findings have been confirmed by further observations, but my earlier conclusions were unjustified, as will appear below, because it is not possible completely to free the pigment layer from the connective tissue by dissection.

A study was undertaken of the pigment in the formalin-fixed blue scrotal skin of the vervet (*Cercopithecus*). Histological examination reveals that this skin has a very thin, unmelanized epidermis, beneath which there is a layer of dense collagenous connective tissue, and underneath the collagen there is a layer of dermal melanoblasts, which have some collagen bundles between and below them. From the epidermal side the skin looks pale blue, and from the inner side the pigment layer looks blue-black. This applies to both fresh

and fixed material, though the colours are apt to fade as the pigment disperses into the fixing fluid.

A General Electric continuously recording spectrophotometer of the Hardy pattern (Hardy, 1936) was used for constructing reflectance curves from the vervet skin.

Fig. 14*a* shows a preliminary curve obtained from a thick layer of collagenous connective tissue with no pigment in it. The material used for this curve

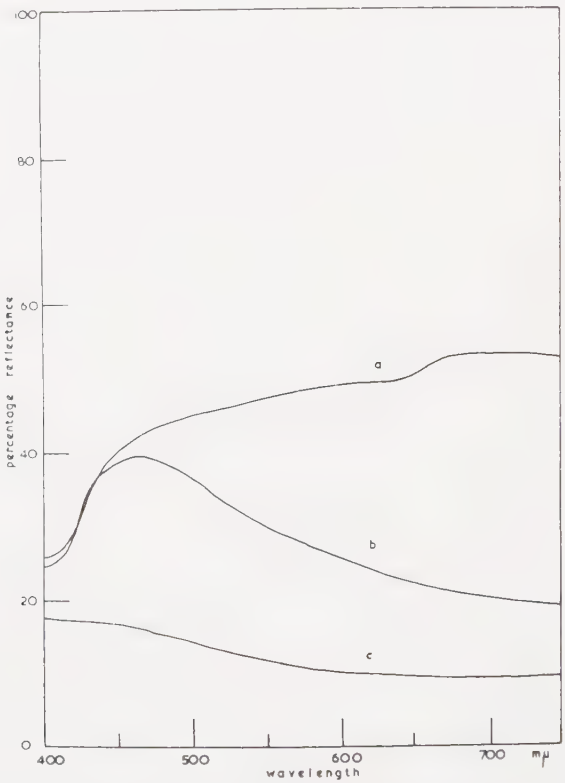


Fig. 14.—Reflectance curves in visible spectrum from (*a*) thick layer of collagen (pig skin), (*b*) external surface of blue *Cercopithecus* skin, (*c*) internal surface of same.

was the formalin-fixed corium of the pig. Strong absorption takes place at the violet end of the spectrum. Fig. 14*b* shows the curve from the external aspect of the *Cercopithecus* scrotum. The initial rise follows precisely that of the collagen, with a peak in the middle of the blue at 462 mμ. followed by a steady descent to the red. Fig. 14*c* is the curve taken from the heavily pigmented internal aspect of the scrotal skin, where the pigment layer is interwoven with and covered by a small amount of connective tissue. Here the surface is obviously dark, but the maximal reflection takes place at the beginning of the curve in the violet-blue region. This is the opposite of the curve

produced by epidermal melanin, in which the highest point is on the right, at the red end of the spectrum (Edwards and Duntley, 1939).

Fig. 15*a* represents the curve of Fig. 14*c* with the vertical scale five times increased, so that the top of the graph lies at 20 instead of 100 % reflectance. Fig. 15*b* shows the reflectance curve from the same aspect of the specimen after immersion for a few minutes in boiling formic acid. An effect of formic acid is to make collagen bundles more translucent. This is accom-

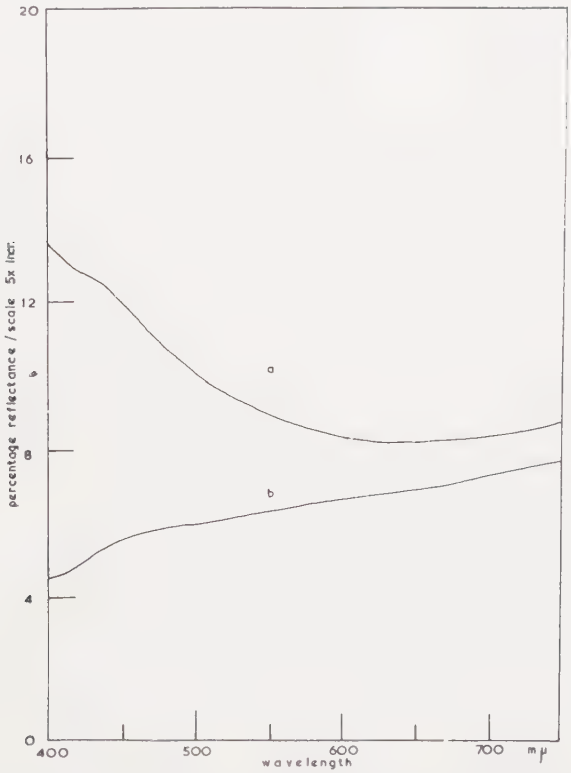


Fig. 15.—(*a*) Same curve as in Fig. 14*c* with vertical scale five times increased; (*b*) from same specimen, after its treatment with formic acid to make collagen translucent.

panied by a considerable swelling of collagen bundles, and histological study confirms that the epidermal and pigment layers remain undisturbed. The curve pattern has now altered to one which could be expected from melanin.

Fig. 16*a* shows the same curve as Fig. 14*b* with its blue peak of external reflectance, and Fig. 16*b* is the curve obtained from the same side of the specimen after its treatment with formic acid. The blue colour has entirely disappeared, and one obtains again a curve like that of melanin influenced to a less extent by the connective tissue.

The colour analysis presented above makes it clear that the collagen plays

the major part in determining the blue colour of these pigment deposits. It does this by absorbing violet, reflecting blue, and transmitting the rays from green to red to the pigment layer which absorbs them. This mechanism probably also applies to the blue colour produced by many dark objects when they are covered by a thin layer of collagen.

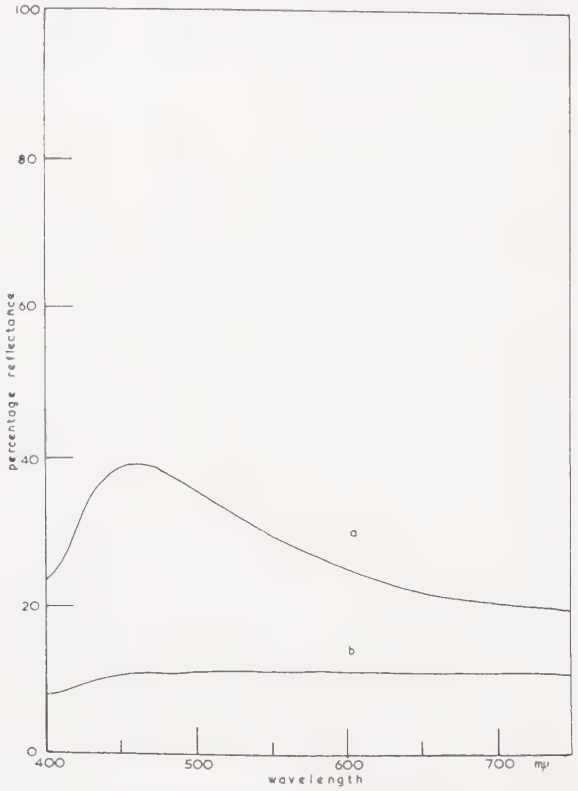


Fig. 16.—(*a*) Same as Fig. 14*b* ; (*b*) Curve after treating specimen with formic acid.

Summary.

Dermal melanoblasts are shown to possess an intricate network of cytoplasmic fibrillae, called melanoglia in the present work. Melanin granules form in intimate relationship with these fibrillae. This would presumably prevent migration of pigment granules while the cell remains intact. It is suggested on morphological grounds that fixed dermal chromatophores are really the same sort of cell as melanoblasts, and that they receive their pigment in a non-granular form through syncytial connections with melanoblasts. Evidence is advanced for the view that the dermal melanoblast is a nerve cell situated at the periphery of the vegetative nervous system. Spectrophotometry of tissue containing dermal melanin shows that its blue colour depends largely on an optical combination of melanin with collagen. Collagen reflects blue and absorbs violet, while the melanin absorbs a relatively large proportion on the red side of the blue. This isolates a blue reflection from the collagen.

I wish gratefully to acknowledge the assistance throughout the present work of Professor Cecil Jackson and Dr. E. J. Marais.

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THE OCULAR MANIFESTATIONS OF ROSACEA.

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WHILE the skin manifestations of rosacea have received respectably antique mention in medical and secular literature (Rolleston, 1933), the first report of its ocular implications seems to be as recent as 1864, when Arlt (1864) described conjunctivitis and keratitis as possible complications. Since then a very considerable volume of ophthalmic literature has accumulated on this subject, in which there appears to be some confusion of thought, and unfortunately no finality, nor even unanimity of view as to aetiology or as to the best method of treatment.

Of the clinical ocular manifestations the first two are relatively unimportant, and are not germane to any consideration of the fundamental nature of the disease; they may be dismissed briefly. Blepharitis is not uncommon; it is characterized by thickening of the lid margins, a scaly desquamation of the skin especially round the lash follicles and dilatation of the superficial skin vessels. Chalazia frequently, and styes occasionally, occur as concomitants. This type of blepharitis occurs more frequently in patients with marked seborrhoea; it improves on treatment for the skin condition and for the associated secondary infection of the lid margins and lash follicles.

The second ocular concomitant is a diffuse hyperaemic conjunctivitis; this occurs most frequently in association with blepharitis, and shows itself by a generalized injection of the conjunctival vessels and a scanty watery discharge. Occasionally with this conjunctivitis there occur small marginal catarrhal ulcers; these ulcers are quite different from the true rosacea keratitis presently to be described. They are confined to the margin of the cornea, do not, even with relapses, advance towards its centre, and when healing very rarely become vascularized. It appears likely that it is very largely the acceptance of these as a specific manifestation of rosacea that has led to the advocacy of riboflavin deficiency as its cause—these ulcers heal readily with the local use of antibiotics lethal for staphylococci, and with the general administration either of riboflavin alone, or with other constituents of the vitamin B complex. They do, however, occur frequently in the complete absence of rosacea, and they indicate only a staphylococcal infection of the conjunctiva together with a low degree of resistance of the patient. I do not think that either they or the blepharitis should be regarded as specific complications of rosacea, nor should any conclusions be drawn from their response to treatment. The conjunctival congestion

may well have the same underlying cause as that responsible for the skin vasodilatation, but, in part at least, it is due to secondary infection from the lid margins, and it also will not be considered any further.

The other ocular concomitants of facial rosacea comprising nodular infiltrations of the conjunctiva, episcleral tissues and of the cornea appear, however, to be specific to the disease and are never seen in the absence of typical skin lesions —or at least a history strongly suggestive of their previous occurrence. This applies particularly to the corneal changes, which both in the active stages and later when the lesions have healed, are pathognomonic, giving an appearance never seen except in rosacea. The nodular conjunctivitis and episcleritis are both rare ; nodules develop in the exposed inter-palpebral region usually near the corneo-scleral junction (Fig. 1), and become surrounded by dilated vessels which persist after the nodules have disappeared, leaving permanent evidence of their previous existence. They appear and disappear very rapidly and may ulcerate. Pathologically, they are similar in structure to the infiltrates in the cornea.

Severe rosacea keratitis is, of course, the most serious and crippling manifestation of the disease as a whole, leading in many cases to considerable impairment of vision. It begins as a symptomless peripheral vascularization of the cornea ; in the more serious cases this is followed by the development of subepithelial infiltrates in the superficial layers of the cornea which form in those zones of the cornea just internal to the vessels, that is, in avascular areas of the cornea (Fig. 2). These infiltrates are confined almost exclusively to the lower two-thirds of the cornea, that is to the area exposed when the lids are open. They are not, to begin with, ulcerated, but in most of them the sodden, superficial epithelium is rubbed off by the lids, or ulceration occurs as a result of secondary infection. These nodular infiltrates heal and vessels grow into the scarred area from the periphery of the cornea, but one of the most characteristic features of rosacea keratitis is its tendency to relapse—a tendency which persists in spite of all forms of treatment, and which may still be present even when all signs of activity in the skin condition have died away. In the relapses the fresh infiltrates appear, not in the old scar, but once again just beyond the margin of the vascularized area, a little nearer to the centre of the cornea. After several mild attacks or even after one severe one, a series of wedge-shaped scars is left around the lower half of the corneal periphery, the tips of the wedges pointing to the centre of the cornea, and interfering with vision more or less seriously, depending on how far they encroach on the pupillary region (Fig. 3). With the more severe ulcers, and particularly if secondary infection be present, perforation of the cornea with the complications attendant thereon may take place, involving even the loss of the eye. Because of the tendency to relapse and because of the extensive vascularization of the cornea in those cases in whom vision is seriously affected, such operations as corneal grafting are of no

FIG. 1.—Left eye of a woman aged 63 showing marginal corneal vascularization and an episcleral rosaceous nodule at the inner side of the eye.

FIG. 2.—Left eye of a man aged 56 showing early nodular infiltration of the cornea which is developing just internal to the vascularized zone.

more than temporary benefit as the graft itself fairly rapidly becomes scarred and opaque.

There are points in this brief record of the clinical evolution of the disease, and in regard to its pathology, which will be considered more fully in later parts of this paper.

Incidence and Specificity.

I think it is impossible for either a dermatological or an ophthalmic clinic working separately to assess the incidence of ocular complications. My impression is that the minor ocular concomitants, blepharitis and conjunctivitis, are

Fig. 3.—Left eye of a woman aged 35 showing in the lower two-thirds of the cornea a series of wedge-shaped scars at the periphery with, in the centre of the cornea, a collection of more recent circular scars.

common, while severe keratitis is comparatively rare. The only figure which I have been able to find in the literature is given by Thygeson (1951), who gives a figure of 5% for the incidence of severe keratitis. My own paper is based on a study of the literature, and examination of the records of 56 patients with severe keratitis who have attended the Middlesex Hospital within the past 15 years, the great majority of whom I have seen myself. These patients only have been considered because, for reasons given earlier, severe keratitis is the only absolutely specific ocular concomitant of facial rosacea. Of these 56 patients, 43 (76·8 per cent.) were women, a figure which agrees broadly with those quoted in other papers, and the age at which keratitis developed ranged from 23 to 69 with an average of 45. All had, or had a history suggestive of, the typical cutaneous lesions. In a few the development of cutaneous and

corneal lesions was almost synchronous, and in those cases with an early development of keratitis the corneal infiltration and subsequent scarring were very severe. In 30 of the patients keratitis developed within two years of the appearance of the facial lesions; in the others the time interval was longer, extending in two cases to 12 and 15 years.

All the patients whose notes I have analysed have had more than one attack of keratitis: one indeed had a history of attacks practically every year for 25 years. A curious feature of the incidence of the attacks of keratitis, both of the initial attacks and of the subsequent relapses, is the marked seasonal incidence which is shown in Table I, in which are analysed the dates of onset of 117 attacks of severe keratitis observed in patients actually attending hospital. This seasonal incidence is confirmed in taking the history of earlier attacks, when patients almost invariably say that their eyes give them trouble in spring

TABLE I.—*Seasonal Onset of Attacks of Rosacea Keratitis.*

January	2	August	10
February	4	September	7
March	13	October	0
April	20	November	2
May	27	December	1
June	17		
July	14	*Total*	117

or early summer. The severity of the ocular lesions is in general not related to that of those of the skin, more particularly in the later relapses; indeed, fresh outbreaks of keratitis not infrequently occur when the skin condition has been more or less completely cured by time or treatment. The tendency of the keratitis to relapse is a marked feature of the corneal condition, which is not influenced by any form of treatment to the eye (except perhaps radiotherapy), or to the skin of the face or of the patient's general condition.

Rosacea keratitis therefore, once it has developed, progresses quite independently of the skin condition. If, however, we regard, as we must, this form of severe keratitis as a specific manifestation of rosacea, it is only reasonable to postulate that both the ocular and the cutaneous lesions have the same essential underlying cause, and it should be interesting and may be useful to compare and correlate clinical, pathological and experimental observations and the results of treatment from the ocular and cutaneous aspects.

The first point to consider is the nature of the peripheral corneal vascularization, which is always a precursor of the more severe nodular infiltration of the cornea. The mechanism of corneal vascularization has been discussed recently by Ashton and Cook (1953). The factors involved are by no means clear, but certain points may be relevant. In the first place congestion of the pericorneal

vessels *per se*, even of considerable duration, is very rarely, if ever, associated with corneal vascularization and this would seem to rule out the possibility that the initial corneal lesion is the result of facial and conjunctival vasodilatation such as might result from psychological causes.

In the view of Ashton and Cook the essential preliminary to invasion of the cornea by blood vessels is a reduction of the compactness of the cornea, accompanied by the stimulus of some growth-promoting substance resulting from injury to the tissues; some causes for this may be inflammatory or metabolic either of which may have an adverse effect on a tissue like the cornea, whose need for oxygen is, even under normal conditions, only barely met. At this point may be discussed riboflavin deficiency, whose rôle in the causation of rosacea keratitis has been enthusiastically advocated (Johnson and Eckardt, 1940; Conners *et al.*, 1943; Tulipan, 1947); these authors emphasize the similarity of the corneal lesions in man to those developing in riboflavin-deficient rats in which marginal corneal vascularization develops as an early sign. It has been pointed out, however, that the marginal vascularization of rosacea differs from that occurring in riboflavin deficiency (Sydenstricker *et al.*, 1940; Fish, 1943, 1944), and the clinical claims that riboflavin alone, or with other components of the B complex, alleviates the corneal lesions arise, I think, from confusion between the specific nodular corneal infiltration and the non-specific marginal ulceration. It is my, and I think the general, experience that the former is not influenced to any marked extent by vitamin therapy. In spite of this negative evidence, however, it may be worth while to note that superficial corneal vascularization may result experimentally in young rats from amino-acid and protein deficiency (tryptophane, Totter and Day, 1942; Buschke, 1943; Albanese, 1945; lysine, Hock *et al.*, 1945; methionine and protein, Sydenstricker *et al.*, 1946), and that from the published reports such vascularization, while being superficial, is not precisely similar to that occurring in riboflavin deficiency, and appears to resemble that seen in rosacea. It is, however, obviously unwise to argue too closely from experimental to clinical findings, and it is to be remembered that corneal vascularization is not a feature of even gross human dietary deficiency. In rosacea keratitis my own series of cases, the general medical evidence of most of which has been carefully assessed, and, I think, the general experience (Sobye, 1950), afford no evidence that obvious metabolic anomalies, such as, for example, other evidence of riboflavin deficiency occur. It will be remembered that the original view of Ryle and Barber (1920) that rosacea was generally associated with anomalies of gastric secretion was subsequently controverted by Brown and his associates (1935), nor is it found in practice that rectification of gastric hypo- or hyperacidity has any influence at any rate on the ocular evolution of the disease.

The next point to consider is the nature of the specific nodular infiltrations developing in the episcleral tissues and in the cornea. The pathological nature

of these infiltrates has, for fairly obvious reasons, been studied only rarely, but although they occur in both vascular and avascular tissues the essential changes are the same. The nodules, whether in the cornea, the conjunctiva or the episclera are composed in the early stages of lymphocytes, plasma cells, epithelioid cells and a few multinucleated giant cells. Later there is proliferation of fibroblasts and invasion by newly formed blood vessels. In the cornea the overlying epithelium is degenerated and desquamates and the superficial layers of the cornea are destroyed, being eventually replaced by a thinner layer of fibrous tissue, in the superficial zones of which run fine blood vessels, and which is covered by a layer of epithelium of irregular thickness. Cultures taken from the centre of these nodules have grown nothing (v. Szily, 1929).

The pathological changes in these nodular infiltrations are therefore non-specific, but they resemble very closely those found in phlyctenular disease, which is generally regarded as an allergic manifestation. It seems quite clear that no particular bacterial infection is constantly associated with rosacea keratitis; several of my patients have had conjunctival swabs which have grown, as a rule, nothing other than staphylococci and diphtheroid bacilli, both of which may be regarded as normal commensals, if not of the conjunctiva, at least of the lid margins. It is true that some part of the symptoms, and of the more unfortunate sequelae such as dense scarring of the cornea or the perforation of a corneal ulcer, may be attributed to secondary infection and that such can be alleviated by appropriate treatment of the skin and conjunctiva (Wise, 1943). The almost constant presence of staphylococci, and an analogy with phlyctenular disease, suggests the possibility that an allergy to the staphylococcus toxins may play some part in the aetiology of the ocular condition; so as far as I can find from a study of the literature this possibility has not been investigated, but it may be worthy of attention.

In regard to allergy, the patients suffering from rosacea keratitis do not, in general, give any history suggestive of the allergic state. The only investigations along these lines which seem to have been carried out are those by Walker (1948) who gives no details, and those into endogenous allergy to the patient's own hormones, the results of which have been equivocal and far from convincing (Zondek *et al.*, 1947; Knape, 1950). Antihistamine drugs systemically are of no help and, locally, give no more than temporary subjective benefit. The results of using cortisone, hydrocortisone and ACTH systemically are also equivocal; the few cases treated with these drugs which have been reported have not been controlled, and other methods of treatment have been used as well (Sutton, 1952; Kalmin, 1952; McDonald *et al.*, 1953). Again, while cortisone used locally is of value in many cases (Duke-Elder, 1951), perhaps more subjectively than objectively, no inferences may be drawn from this, for it is known to be of equal or even greater value in many other corneal conditions be they of known bacterial or virogenic, or presumed allergic origin.

The next point in the clinical evolution of the ocular changes which calls for consideration is the marked seasonal incidence, which I gather is generally more striking in the ocular than in the cutaneous lesions, although Sobye (1950) has noted that of 128 patients attending a dermatological clinic in Copenhagen, 85 (66·4 per cent.) first applied for treatment in March, April or May, the remainder being spaced fairly evenly over the remaining nine months of the year. So far as the eye is concerned an analogy with spring catarrh may come to mind, and it is conceivable that external allergens such as pollens may irritate an eye already sensitized by other factors. The general appearance of the eye, however, differs from that seen in other definite allergic reactions as from drugs such as atropine, nor as has been pointed out earlier does there seem to be any definite evidence inculpating an allergic cause.

The other obvious possible factor is some form of photosensitization, which, however, as far as I know does not occur in any other ocular disease. Sobye (1950) suggested that the effect of light on the vessels of the skin may play some part in the cause of the facial eruption. Experimentally he found that exposure of the skin of these patients to ultra-violet light gave normal reactions, but as he himself points out, the skin exposed was not on the face but on the abdomen, and the only conclusion that should be drawn, therefore, is that rosacea is not of the same nature as the chronic polymorphous light eruption.

So far as the eye is concerned, neither the wearing of dark glasses, nor in the very few cases of which I have heard (Ridley, 1953) the wearing of contact lenses, does anything to prevent recurrence of the corneal lesions. My impression is, however, that mepacrine is of some help, at any rate subjectively in a proportion of the cases, and this is borne out by Hudson (1953), who has treated a controlled series of about 50 cases. He states that about half of the patients given mepacrine showed quite marked subjective improvement: a few of them stated that for the first time for years they had been able to take a summer seaside holiday without almost intolerable ocular discomfort. It appears, however, to have little or no effect on the clinical evolution of the keratitis itself and so far as I know the only *modus operandi* suggested is that the yellow staining of the skin and conjunctiva which it induces acts as a filter cutting off the short visible and the ultra-violet rays of the spectrum. An odd point which may be mentioned here, although I do not know that any conclusions can be drawn from it, is that Wise (1943) and other American writers state that rosacea occurs rarely, if ever, in negroes.

I propose to say very little about treatment. A careful overhaul of the patient's general medical condition, the rectification of digestive upsets, the elimination of gross focal sepsis, treatment to the skin condition and the administration of vitamin B complex do a great deal to improve the minor ocular concomitants of rosacea, the blepharitis, conjunctivitis and marginal corneal

ulcers, but however helpful and co-operative our dermatological and physician colleagues are, their efforts are no more fruitful than our own in influencing the course of a severe keratitis. In this last type of case the local ocular treatment follows the usual lines and need not be considered, but I should like to emphasize the value of radiotherapy. This has been advocated by Greeves for at least 25 years, and is most useful if given in the early stages of an attack of keratitis when it helps to quieten the eye, to abort the active infiltrative process in the cornea, and to minimize the subsequent visually damaging scar formation. Fifty-four of my 56 patients have been treated by this method by Windeyer at the Middlesex Hospital (see Greeves *et al.*, 1947), x-rays being applied to the cornea by cross-fire, with a total dosage to the cornea of 400 roentgens given in 4 divided doses at weekly intervals. One patient has had 8 courses and two others 6 each; no ocular complications, such as cataract, have been seen. Eight patients failed more or less completely to show any improvement but including these the average period free from relapses after radiotherapy has been 2·2 years. Twenty-four patients have been free from relapses for periods of 3 years or longer after one or more courses of treatment, several of these having previously had annual attacks. The longest periods of freedom have been 10, 8, 8 and 7 years. On the whole, therefore, it seems that local radiotherapy will be successful in about half the patients treated, and may be expected to give them periods of 3 years or longer free from relapses. If and when they do relapse further treatment can be given and equally good results anticipated.

Finally, I do not think that any definite conclusions can be drawn from this study of the ocular aspects of the disease, but a few points which may be made are :

(i) Minor ocular troubles—blepharitis, conjunctivitis and marginal ulcers—are common in rosacea, but they are not specific to the disease, and no inferences should therefore be drawn as to its fundamental nature from their clinical course and response to treatment.

(ii) Severe keratitis is specific and although, once having developed, it may progress quite independently of the skin lesions, it must be assumed that both have the same pathogenesis.

(iii) The corneal vascularization which is a precursor of keratitis cannot occur as a result of pure vasodilatation ; there is some experimental evidence but no clinical evidence that it may result from gross metabolic disturbances.

(iv) There is no evidence that bacterial infection plays any part other than in making an already existing condition worse.

(v) The pathological appearances are non-specific, and there is no valid evidence to suggest that the ocular disease has an allergic basis.

(vi) Some seasonal factor, probably photosensitization, appears to play an important part, although in what way is not yet known.

(vii) The most effective form of treatment for the severe ocular lesions at present available seems to be local radiotherapy.

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ROSACEA WITH SPECIAL REFERENCE TO ITS OCULAR MANIFESTATIONS

PETER BORRIE.

The lack of knowledge concerning the clinical correlation between ocular and cutaneous rosacea is an example of the price we have to pay for the increasing specialization of medicine. Such information as we have has been obtained from the study of rosacea patients attending exclusively, or, at any rate, in the main, either the skin or the eye department. Only two published series concern patients from both departments, though of Doggart's (1931) 78 cases, 65 came from the eye department. Wise (1943) analyzed an equal number from each category, but this series comprised only 60 patients in all.

How misleading information can be, when obtained by studying one or other group of patients, is shown by the incidence of ocular rosacea found in patients attending the skin department of a general hospital, as compared with that of an eye hospital, seen by the same observer over the same period of time. Thus, of 134 consecutive patients seen in the general hospital, only 4, or 3%, had ocular manifestations: whereas, in the eye hospital, ocular symptoms were found in 99 of 104 consecutive patients, a percentage of 95·2.

This disparity in the incidence of ocular rosacea may be accompanied by similar conflicting evidence with regard to sex, age, and the relative time of onset of the two components of the syndrome. Indeed, unless some such explanation exists, certain published reports must be entirely apocryphal. The present communication, therefore, concerns the analysis of the two groups of patients already alluded to. It is limited, however, to 130 consecutive patients, none of whom had ocular lesions, referred to as Group A, seen in the general hospital: and 99 patients suffering from both cutaneous and ocular rosacea, referred to as Group B, seen in the eye hospital. To complete this type of investigation, a third series should have been studied, comprising patients suffering from ocular rosacea alone. However, in view of the conflicting opinions concerning the criteria on which such a diagnosis should be based, this proved impossible.

Table I shows the sex and age incidence of rosacea, with regard to both the cutaneous and ocular manifestations. In the case of the purely cutaneous cases, the sex incidence agrees with previous reports, men being affected in less than a third of cases. However, when the eyes were involved as well, 43·5% of the cases were in men. The age at onset of the skin lesion was usually between 20 and 49 years in women when the skin alone was involved, though a fifth of the cases began in the sixth decade when the eyes were also affected.

TABLE I.—*Sex and Age Incidence.*

	Group A.			Group B.							
	Women.		Men.		Women				Men			
				Skin %		Eyes %		Skin %		Eyes %	
Age.	%.		%.								
10–19	5·3		9·2	3·6		1·8		11·6		2·3	
20–29	23·4		22·0	18·0		14·3		25·6		25·6	
30–39	35·4	84·8	27·0	19·8	67·8	25·0	69·3	25·6	74·4	14·0	72·1
40–49	26·0		27·0	30·0		30·0		23·2		32·5	
50–59	8·6		13·5	21·5		25·0		7·0		18·6	
60–69	0		0	3·6		3·6		7·0		7·0	
70–79	1·3		1·3	3·6		0		0		0	
Total.	71.5		28.5	56		56·5		43		43·5	

In men the onset of the skin lesion was more evenly spread over the second to sixth decades, whether the eyes were involved or not. In the majority of cases the ocular lesion began during the third to sixth decades, irrespective of sex.

TABLE II.—*Duration.*

	Group A.			Group B.							
	Women.		Men.		Women.				Men.			
				Skin %		Eyes %		Skin %		Eyes %	
Years.	%.		%								
Less than 1	33		30·0	10·75		25·0		11·65		18·6	
1–5	46·6		48·5	44·45		36·5		32·7		33·2	
6–10	17·2		18·8	17·8		16·2		18·6		18·6	
11–15	3·2		0	10·75		8·8		11·6		7·0	
16–20	0	3·2	0	8·8	26·9	3·6	21·2	11·6	37·2	9·3	18·6
More than 20	0		2·7	7·3		8·8		14·0		2·3	
Maximum	15 years		30 years	30 years		38 years		43 years		37 years	

Table II shows the duration of the disease when the patient was first seen. The fact that relatively more patients were seen from Group A than Group B during the first year of their malady must be explained by the fact that the skin department of the eye hospital is an innovation, and so a great number of old cases, which had been attending the hospital for long periods, were seen initially. This does not, however, explain the many more patients attending the eye hospital more than 10 years after the onset of the disease as compared with those attending the general hospital.

TABLE III.—*Ocular Manifestations.*

Disease.	Women %.	Men %.
Blepharitis	5·3	7·0
Conjunctivitis	3·5	2·0
Episcleritis	3·5	0
Keratitis	87·7	84·0
Iritis	0	7·0

Table III shows the incidence of the various ocular manifestations. For the sake of lucidity I have given only one diagnosis to each patient—that of

the most severe ocular lesion from which he was suffering. The number of patients suffering from blepharitis and conjunctivitis is much lower than in other published series. All these patients were referred to me by ophthalmologists, and it may be that, if the mild ocular condition responded quickly to treatment, and the facial lesion was not troublesome, other similar patients may not have been referred at all.

In the patients suffering from blepharitis alone there was a severe degree of seborrhoea. The blepharitis had persisted for periods of up to 15 years, without the supervention of any further ocular complications, suggesting that it was the result of the seborrhoea rather than of the rosacea.

Keratitis was by far the commonest complication, but I am not in a position to state whether all these cases fulfilled the strict criteria advocated by some ophthalmologists for the diagnosis of true rosaceous keratitis.

In the cases of episcleritis and iritis, these were the only abnormalities present in the eye, the former occurring entirely in women and the latter only in men.

TABLE IV.—*Relative Onset of Cutaneous and Ocular Manifestations.*

	Women %.		Men %.	
Simultaneous	28·5	.	25·6	
Skin first	48·1	.	58·0	
1–5 years previously . .		30·1		21·0
6–10 „ „ . . .		10·8		23·0
> 10 „ „ . . .		7·2		14·0
Eyes first	23·3	.	16·4	
1–5 years previously . .		10·7		11·6
6–10 „ „ . . .		5·4		2·4
> 10 „ „ . . .		7·2		2·4

Table IV shows the time of onset of the ocular and cutaneous manifestations, relative to each other. This is probably the most important table of all, because it shows that the ocular manifestations began first in almost one-fifth of cases. Moreover, they preceded the skin lesion by periods of up to 30 years. In over a quarter of the patients skin and eye signs began simultaneously. The sexes again behaved similarly, except that the eye signs tended to occur first more often in women than in men.

DISCUSSION.

Certain clinical facts emerge fairly clearly from this investigation. With regard to the sex incidence of rosacea, ocular manifestations are relatively commoner in men. Wise made the same observation, the sex ratio in all his 60 cases being 2 females to 1 male, whereas, in those with ocular complications, the incidence was equal. In the present series the percentages were, for cutaneous rosacea alone, 28·5% men, ocular and cutaneous lesions, 43·5% men, making an overall incidence of roughly 1·8:1 women to men. There was no real difference between the sexes with regard to age of

onset of the disease, though the ocular manifestations occurred first more commonly in women. The duration of the malady was not markedly different as between men and women, except that, when both components of the condition were present, the cutaneous lesion tended to persist longer in men, 25·6% of whom had had facial erythema for more than 15 years, as opposed to 16·1% of the females. My clinical impression is that men are certainly more difficult to treat than women. Finally, the various types of ocular complications occurred with equal frequency in the two sexes, with the exception of episcleritis, which was seen only in women, and iritis seen only in men.

There was little difference in age at onset between the ocular and cutaneous lesions, though the former were less common in the 2nd decade and more common in the 6th and 7th. In the majority of cases the disease began between the ages of 20 and 60. That the disease appeared to last longer when the eyes were involved must be largely due to the fact that the severity of the ocular symptoms demands constant treatment. Nevertheless, if the treatment of the skin is persisted in relapses are greatly diminished, but this does not appear to be so with regard to the eyes.

Keratitis, as has been previously reported, is by far the commonest ocular manifestation, accounting for over 85% of all the cases in the present series. In the 3 cases of iritis there was no other ocular abnormality, which suggests that it may be a true rosaceous manifestation, Doggart (1931) having stated that it is only a complication of a severe keratitis. Doggart also found blepharitis in all his cases, and suggested that this may have rendered possible the extension of the disease from the face to the eyeball. However, in the present series, blepharitis was frequently seen without any other ocular manifestation, even when it had been present for 15 years. The extension, therefore, assuming it does take place in the manner suggested, is a slow process. Further, it appeared that the blepharitis, when present without other signs of ocular involvement, was the result of the severe accompanying seborrhoea rather than of the rosacea.

With regard to the relative time of onset of the ocular and cutaneous lesions, in approximately 20% of cases the eyes were first affected, in 27% both lesions appeared together and in 53% the cutaneous lesion appeared first. Either lesion could precede the other by anything up to 30 years. Doggart (1931), Wise (1943) and Klaber and Wittkower (1939) all state that the eye signs invariably follow those of the skin, the latter authors also stating that they are consequent upon long-standing facial congestion.

No constant correlation was found between the acute ocular and cutaneous exacerbations, though the skin tended to be worse in the summer. In a few individuals they did occur together, but these constituted a small group in whom symptoms of the disease appeared for a few weeks every spring, only to

disappear completely for the rest of the year. Doggart (1931) found that cutaneous and ocular relapses coincided. In the present series, however, no definite correlation could be seen between the severity of the skin and eye lesions. On the whole, the impression was gained that the cutaneous signs were more severe when the eyes were not involved.

To sum up the clinical facts, therefore, it appears that a chronic erythema of the face and certain specific ocular changes frequently occur together in the same patient; that this patient is more likely to be a woman than a man; and that, though the two halves of the syndrome may not commence together, the skin being affected first in the majority of cases, the age of onset is roughly the same. Apart from these scanty facts, I can find no further clinical correlation between ocular and cutaneous rosacea.

Little information is gained from consideration of the treatment of cutaneous rosacea. In the present series satisfactory improvement was obtained from local applications alone in about 75% of the cases, and in these patients additional x-ray therapy did not increase this improvement. In the remaining 25%, mostly men, the disease responded poorly to all forms of therapy, including x-rays. Thus, in my experience, x-ray treatment does not appear to have the same beneficial effect on the skin as it does on the eyes.

A small controlled series of cases (Borrie, 1952) treated with mepacrine showed little, if any, improvement. However, I cannot say whether this treatment does or does not decrease the patients' sensitivity to sunlight. It does appear to have this effect on the ocular lesion. The general consensus of opinion among my patients was that they would rather be pink than yellow.

Consideration of the pathogenesis of the disease again does not help much in explaining the association of the skin and eye lesions. The suggestion, however, that the ocular lesion may be associated with an allergy to the staphylococcus is interesting. Aron-Brunetière and his colleagues (1952) had the same idea with regard to the skin lesion and saprophytic organisms, when they treated the disease with chloramphenicol; their satisfactory results have been confirmed by other workers both on the Continent and in America. Sobye (1949) showed that the abdominal skin of rosacea patients was not more sensitive than normal to light, and my own investigations, with regard to ultra-violet light and the facial skin, had the same results. However, I have been struck by the high percentage of rosacea patients who state that they always avoided the sun, even before the onset of their malady, because they failed to go brown, turning a brilliant and somewhat unbecoming pink. Thus a failure of melanogenesis may play a part in causing persistent facial erythema and, possibly, a lack of some similar protective mechanism in the eye may explain the ocular seasonal fluctuations.

Further discussion of the pathogenesis of rosacea would not be pertinent in the present context, despite the fact that the wealth of unsubstantiated

hypothesis on this subject varies from something alkaline in the stomach to something horrid in the cowshed. Suffice it to say, in conclusion, that the cutaneous and the ocular lesions of rosacea are clearly independent of each other, and that the disease does not spread from the face to the eye or vice-versa. The pathogenesis must consist of a mechanism capable of affecting each tissue in a specific manner, the degree to which each is affected in any given case probably depending upon superadded constitutional factors. Such a concept is not without precedent, and calls to the mind the role which, it has been suggested, the pituitary thyrotropic hormone plays in malignant exophthalmos and localized myxoedema.

Summary.

1. One hundred and thirty patients suffering from cutaneous rosacea and ninety-nine patients suffering from both cutaneous and ocular lesions were analyzed.

2. The positive findings were that ocular lesions were relatively more common in men; that the cutaneous lesion appeared first in 53% of cases and the ocular in 20%, and that each could precede the other by anything up to 30 years; and that while keratitis was by far the commonest ocular manifestation, iritis did occur without a preceding keratitis and blepharitis alone was probably secondary to seborrhoea and not to rosacea.

3. It is concluded that the cutaneous and ocular lesions of rosacea, though having the same basic cause, are otherwise independent of each other, and that the disease does not spread from the skin to the eye or vice-versa.

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SECTION OF DERMATOLOGY

19 March 1953

A Case of Persistent Peri-orbital Oedema.—Dr. J. Overton.

A. F—, male, aged 48 years.

Work.—Engineer ; assembles knitting machines ; handling chrome nickel.

Previous history.—For a number of years has had symptoms suggesting mild paroxysmal rhinorrhoea.

Family history.—No hay-fever, asthma, or skin trouble.

Personal history.—Never been abroad.

Present history.—A year ago developed swelling of the right lower lid. This gradually increased, and soon involved the left lower lid. Subsequently the upper lids have been involved, and, more recently, the forehead. The process has been symptomless and varied initially in intensity. No history of cracks round eyes or nose. No nasal discharge. General health has been satisfactory. During the last three to four months patient has noted a persistent unpleasant taste in the mouth, with some abnormal palpable softening of the hard palate. He has recently developed fissures at the angles of his mouth and in the naso-facial folds adjoining the oedematous areas.

Investigations.—No abnormality of eyes. No clinical or ancillary evidence of abnormalities in the cardio-vascular, renal, haematopoietic systems, antra and skull. No evidence of upper respiratory tract disease. Intradermal test for trichiniasis negative.

Examination.—Oedema of both upper and lower lids, extending to a slight degree on to the brow. Mouth : patchy erythema of the hard palate ; bilateral angular stomatitis.

Patch test to denture.—Erythema with burning under the site of application occurred two hours after apposition to skin. This subsequently subsided and cleared completely 24 hours later, though the denture was maintained in position for 48 hours.

Dr. C. H. Whittle : We have two examples in men under observation at the moment. We have not been able to find any fissures and are not any nearer to the aetiology. We tried ACTH over a short period on two occasions and the oedema subsided, but as soon as we stopped the treatment it reappeared. Cortisone by mouth is equally effective.

Dr. F. F. Hellier : Most of these cases have in my experience fissures somewhere and there is some evidence of this here near the eyes. Another possibility is that this patient is sensitive to the material of his dentures. He shows redness of the palate confirming this, and I have seen dermatitis elsewhere on the body clear when such dentures have been removed. Whether sensitization to dentures could produce an allergic reaction of this type is uncertain, but it should be kept in mind.

Dr. H. R. Vickers : These are very interesting and most puzzling cases. I feel that the essential problem is associated with something peculiar to the lymphatic drainage of the central part of the face. I was very interested in his denture sensitivity.

All the cases I described (*Brit. med. J.*, 1949, vol. ii, 1091) and all I have seen since gave the history of wearing their dentures when asleep. This is the only case I have seen in which denture sensitivity has developed in a patient who normally takes his teeth out at night, and I think this indicates that this particular man became sensitized very easily.

Recurrent Painful Swellings of Shin.—A. Jarrett and W. N. Goldsmith.

B. F—, female, aged 35.

Occupation.—Shop assistant.

History.—Since the age of 21 years patient has had recurrent painful swellings on the anterior aspect of the left lower leg. The right leg has been swollen, but patient denies that she has had any painful swellings on this leg. The legs were blue and cold, and this was worse during the winter. The circulation has improved after bilateral lumbar sympathectomy.

The swellings usually occur as soft painful areas, which then become red and extremely tender. After about two weeks they subside and the underlying skin sometimes becomes hard and indurated, or it may return to its original state. The attacks occur at approximately two-monthly intervals.

Family history.—*Nil* relevant.

General health.—Good.

Treatment.—Bilateral lumbar sympathectomy about 13 years ago.

Seven years ago two further operations, which are presumed to have been peri-arterial stripping of both femoral arteries. Course of P.A.S. and streptomycin.

Streptococcal vaccines from organisms in throat. Several courses of antibiotics with temporary benefit. Also has had calciferol, vitamin K, thyroid and occlusive dressings.

Investigations.—W.R. and Kahn negative. Plasma proteins: Total 6·75 g. %; albumin 5·0 g. %; globulin 1·75 g. %.

Earlier biopsies: non-specific inflammatory reaction with large amount of fibrosis. Not typical of Bazin's disease. Recent biopsy essentially the same. No acid-fast bacilli seen. Mantoux, March 1950, 1 : 10,000 strongly positive.

Skiagram of chest normal. X-ray examination of teeth and sinuses: nothing significant found. Urine—N.A.D. Blood sugar curve normal. Blood: Hb 90%. White cell count 7800, neutrophils 66·5%, lymphocytes 26%, monocytes 6·5%, eosinophils 1%. Blood cholesterol 190 mg. %. Basal metabolic rate 16%.

Dr. W. N. Goldsmith: When I first saw her there was a little stiff plaque which made me think it might be necrobiosis lipoidica. For quite a long time afterwards in hospital nothing more happened except that a biopsy was done, and subsequently a little soft swelling appeared just under the wound, and, later, similar ill-defined boggy swellings have appeared in the neighbourhood. There is a certain amount of diffuse oedema of the leg, and, of course, there is a history of vascular disorder. But these swellings are found only on the front of the left leg. We wondered whether they could possibly be artefacts. The patient had previously been placed in plaster-of-paris for three weeks.

Dr. F. F. Hellier: I support the diagnosis of artefact. The patient resembles one of Dr. Anning's whom I have seen with recurrent swellings of the abdominal wall rather like these. While the patient was in hospital there were no lesions, but when she went out the swellings developed. We never convicted her of artefact, but her husband is a diabetic and she used to give him injections when she was at home, so that the means for creating an artefact in this way were available. One knows how troublesome these artefacts are to detect. It is extraordinary that in this case the lesion should be confined to one leg only.

Dr. Louis Forman: I thought there were significant changes in the small artery in the section. Further, the shape of the nose and forehead with wide spacing of the teeth suggests the possibility of congenital syphilis. It might also be responsible for the vascular changes. It would be worth while giving this patient a course of penicillin injections.

Paraffinoma.—Dr. C. D. Calnan.

L. B—, female, aged 71.

History.—Twenty to thirty years ago in Nuremberg she had injections under the skin of the face, neck and breasts by a Parisian cosmetic surgeon. She is unable to remember precise details of the sites of injections. Gradually since then the present nodules have appeared over the course of many years. They are painless.

Examination.—In the skin of the cheeks, neck, chest and breasts are numerous woody hard nodules and plaques of various shapes and sizes. They are bilateral

but not symmetrical. On the right side of the face over the largest plaque is slight erythema. They are not tender.

Histology (Dr. H. Haber).—The epidermis does not show any appreciable changes. Within the cutis there is only a mild perivascular infiltration consisting of round cells. At the cutis and sub-cutis border there is one cyst lined with foamy histiocytes. The fat tissue shows numerous round and oval cystic spaces lined with vacuolated or foamy histiocytes. Some cysts are outlined by a fine fibrous membrane. Groups of cells which show xanthoma-like foamy appearance, or vacuoles, are also seen. There is also a scattered mild lymphocytic infiltration. Further down there follows a big lump consisting of scleroderma-like fibrous tissue exhibiting many cracks and studded with cysts of different sizes and shapes. Some cysts are surrounded by connective tissue only, some are lined by flattened cells and some show foamy flattened histiocytic cells. There are many vacuolated macrophages, some also showing a foamy appearance like xanthoma cells. Some large cysts are surrounded by a characteristic fibrous capsule, which consists of onion-like lamellae. Large cavernous spaces lined by flattened histiocytic elements and separated from each other by fibrous septa are conspicuous. Staining for fat with Sudan III shows the vacuoles and cysts to contain fat.

Comment.—Most of the cases of paraffinoma seen in this country have followed injections of paraffin usually containing a stimulant. Subcutaneous injections of hard paraffin for cosmetic purposes, once popular on the continent, have been abandoned for so long now that patients like this lady are rarely seen to-day.

The histological picture of oil cysts and condensed collagen in onion-like formation around them is identical with the case of spontaneous sclerosing lipogranuloma I showed here last year.

REFERENCE.

CALNAN, C. D. (1953) *Brit. J. Derm.*, **65**, 28.

Dr. CALNAN: The patient's memory is not very good as to precisely where she had these injections, but undoubtedly she had been injected on the cheeks and breasts. One may get these lesions along the course of the lymphatics and in lymph glands and also elsewhere as metastases. They have even been found internally, though rarely.

Cheilitis Glandularis Apostematosa.—Dr. E. WADDINGTON.

S. B—, male, aged 66.

He complains of scaling of the lower lip and " stickiness " of both lips for 50 years.

Previous history.—About 30 years ago he had a nasal operation for chronic catarrh. This was only partly successful.

Family history.—His sister has a similar condition affecting the lower lip.

Present illness. At the age of 16 he developed scaling and swelling of the lower lip and " stickiness " of both lips. The lower lip feels nodular when he touches it with his tongue and he is able to express sticky fluid from both lips. In addition he has suffered from chronic nasal catarrh for many years.

This condition has persisted unchanged despite much treatment. Recently his own doctor cauterized the lower lip and since then there has been a slight improvement. Abscess formation has never occurred.

On examination.—The lower lip is swollen and everted. When the patient talks his lips appear to stick together.

The entire mucosal surface of the lower lip and the adjacent buccal mucosa are dotted with the dilated orifices of the mucous glands, which are more clearly seen after squeezing the lip, when the mouths of the ducts are marked by droplets of a clear sticky fluid.

Comment.—Cheilitis glandularis was first described by Volkman in 1870. He reported five cases, two of which had lesions identical with those in this patient and the other three were complicated by recurrent abscesses.

Three types are described depending on the degree of secondary infection :

(1) The uncomplicated type, of which our patient is an example.

(2) The superficial suppurative type with crusting and fissuring of the lip.

(3) The deep suppurative type with abscess formation followed by the development of fistulae.

The disease most commonly affects the lower lip, but may also involve the upper lip and the buccal and naso-pharyngeal mucosa, leading to a chronic catarrhal condition of the nose and pharynx.

Sutton believes that there is a congenitally excessive supply of glandular tissue of the lips, mouth, nose and pharynx, and histologically he found an adenomatous condition of the mucous glands with an enormous dilatation and hypertrophy of the ducts. He believes that it is not precancerous, whereas continental dermatologists hold the opposite view. Touraine found 49 cases in the literature, of which 24 had an associated carcinoma of the lip.

I find it hard to believe that this condition is precancerous, and the high incidence of malignancy in some of the reported cases might be explained by the fact that advice is sought only when a carcinoma develops, and the cheilitis glandularis is merely an incidental finding.

It is probable that the simple form of cheilitis glandularis is more common than the literature suggests and is often ignored because of the mild subjective symptoms.

References.

Volkmann (1870) *Virchow's Archives*, **1**, 142.
Sutton, R. L. (1914), *Internat. Clin.*, **3**, 123.
Touraine, A. (1950), *Presse Méd.*, **58**, 1369.

The President : According to the patient's statement the lip has been scaly at times, though his principal complaint is of persistent swelling and stickiness; the lips are glued together in the morning sometimes. It must be the mildest possible degree of cheilitis and presumably never likely to lead to ulceration.

Dr. H. T. Calvert : This condition seems often to be associated with neurodermatitis, and this patient has a patch of neurodermatitis affecting one hip. I regard this condition as a neurosis of the skin.

Dr. Waddington : The cases reported in the literature have not been associated with a neurodermatitis, although the associated exfoliation may be aggravated by the habit of licking the lips.

The following cases also were shown :

Ungual Dystrophy. ? Lichen Planus.—Dr. J. Overton.

Atypical Granuloma Annulare in a Diabetic.—Dr. G. A. Beck (for Dr. C. H. Whittle).

Arsenical Keratoses and Pigmentation.—Dr. C. D. Calnan.

Lichen Nitidus.—Dr. C. D. Calnan.

CURRENT LITERATURE.

MUCOCUTANEOUS JUNCTIONS IN THE RAT IN DEFICIENCY OF PYRIDOXINE. V. Ramalingaswami and H. M. Sinclair. (1953) *J. invest. Derm.*, **20**, 81.

From time to time sore lips and fissures at the angles of the mouth are attributed to deficiencies of, or to be more exact are reported as cured by administration of, various accessory food factors riboflavin, iron, niacin, pantothenic acid and now pyridoxin. Mueller and Vilter are quoted as having produced lesions around eyes, nose and lips by creating a pyridoxin deficiency by means of desoxypyridoxin (60–150 mg. per diem for 2–3 weeks).

Pyridoxin deficiency is recognized as the cause of rat acrodynia, but nobody hitherto has taken much notice of the very conspicuous mucocutaneous lesions produced by these authors in their experiments reported here. About 15 weeks elapse before the signs develop. J. H. T.D.

BLOOD PHENOL LEVEL AFTER TOPICAL APPLICATION OF PHENOL-CONTAINING PREPARATIONS. R. Ruedemann and W. B. Deichmann. (1953) *J. Amer. med. Ass.*, **152**, 506.

Blood phenol levels were estimated after applying to the skin 50 g. of calamine lotion with 2% phenol and 21 g. of phenol-camphor-liquid paraffin ("camphophénique") which contains 4·75% phenol.

The maximum quantity of phenol placed on the skin was equivalent to 4 of these 1 g. doses in 6 hours. Free phenol in the blood rose from a control level of 0·15 mg. to 0·4 mg. per 100 ml. remaining there regardless of whether 1 or 4 doses had been applied and whether it was applied, in the aqueous or the oily medium. The level of conjugated phenol showed some correlation with the dose applied.

The highest isolated concentration of free blood phenol (0·8 mg.) was observed in a person exposed to 3 1-g. doses of phenol in calamine ; the highest level of conjugated phenol was observed after 3 doses of "camphophénique."

Covering the skin with a loose bandage or clothing after the application of one dose of phenol decreases the rate of absorption, but not the total amount absorbed. A. J. R.

ACRODERMATITIS ENTEROPATHICA. C. J. Dillaha, A. L. Lorincz and O. R. Aavik. (1953) *J. Amer. med. Ass.*, **152**, 509.

Danbolt in 1942 proposed the name of acrodermatitis enteropathica for a condition which had previously been reported either as systemic moniliasis or as a variant of epidermolysis bullosa. This condition begins between the ages of 3 and 18 months, runs an intermittent course with partial remissions and increasingly severe exacerbations and may end in death. It is, characterized by crops of vesiculo-bullous lesions grouped around the body orifices, eyes, occiput, elbows and knees and both surfaces of hands and feet, especially between the fingers and toes, and around the nails. Gastro-intestinal disturbances and total alopecia are usually present, and there may be retarded growth and personality changes. Secondary infection of the skin lesions with pyogenic organisms and yeasts commonly occurs.

The authors of this paper review the 20 cases they have discovered in the literature, and report a new case which responded dramatically and completely to oral diiodohydroxyquinoline. The response to this treatment suggests that a gastro-intestinal infection, but not moniliasis, must be responsible for the syndrome. A. J. R.

PENICILLIN ANAPHYLAXIS : NON-FATAL AND FATAL REACTIONS. S. M. Feinberg, A. R. Feinberg and C. F. Moran. (1953) *J. Amer. med. Ass.*, **152**, 114.

Severe and sometimes fatal reactions to penicillin are occurring with increasing frequency. The principal symptoms are urticaria, asthma, shock, cyanosis and unconsciousness. This type of sensitivity (unlike the common delayed urticarial syndrome) is usually induced by repeated courses of penicillin, and occurs more frequently in persons who are subject to other allergies. The immediate wheal reaction with scratch or interdermal testing characterizes this anaphylactic type of sensitivity.

Penicillin should not be given for trivial conditions ; a history of previous administration and reactions should be obtained, and ideally a skin test should be performed. A. J. R.

LONG SURVIVAL IN MALIGNANT MELANOMA. A. R. Galgano. (1953) *J. Amer. med. Ass.*, **152**, 518.

A report of an unusual case of malignant melanoma in which 11 years elapsed between the removal of the primary lesion and the development of pulmonary metastases and a further 9 years before the death of the patient. A. J. R.

LOCAL INJECTION OF HYDROCORTISONE AND CORTISONE INTO SKIN LESIONS OF SARCOIDOSIS. R. D. Sullivan, R. L. Mayock, R. Jones, Jr., and H. Beerman. (1953) *J. Amer. med. Ass.*, **152**, 308.

A careful study of the gross and histological effects of the local infiltration of hydrocortisone and cortisone on the skin lesions of sarcoidosis in 5 patients.

Hydrocortisone produced complete or almost complete regression of all lesions injected. Most of the lesions showed partial relapse after 4–7 weeks. With cortisone there was less complete regression and earlier relapse.

The effect is apparently produced by a direct action on the pathological process.

Cortisone was given orally for 6 weeks to 4 patients. Regression of the lesions occurred more gradually and recurrence was more rapid than with local injection. Rebound relapse occurred in 3 of the 4 patients. A. J. R.

PRIMARY FIBROSARCOMA OF THE SKIN. C. Mopper. (1953) *J. Amer. med. Ass.*, **152**, 570.

Darier and Ferrand in 1924 distinguished dermatofibrosarcoma protuberans as a clinical and pathological entity, although cases had earlier been recorded under other diagnoses. As the terminology is rather confused Mopper prefers the name primary fibrosarcoma of the skin. He adds 5 new cases to the total of over 200 which have now been reported and reviews the literature.

Although the abdomen and back are the commonest sites, this tumour has been described on every part of the skin surface except the palms and soles. The clinical features are variable – there may be a single nodule or an extensive indurated plaque and the surface may be smooth irregular or ulcerated.

Early wide excision is the treatment of choice and the prognosis is then favourable. There may be long survival despite repeated local recurrences. Lymph node and pulmonary metastasis, although rare, can occur. A. J. R.

ALOPECIA LEPROTICA : ITS RELATIONSHIP TO TRANSMISSION OF LEPROSY. E. A. Cleve and F. W. Pruitt. (1953) *J. Amer. med. Ass.*, **152**, 573.

The authors examined 1369 patients with leprosy in Japan, Korea and Formosa. Alopecia leprotica was found in 479 (45%). In these countries it is customary to shave the scalp of newborn infants. In 11 countries where this practice is not carried out the incidence of alopecia leprotica is 0·3%. It is suggested that this great difference in incidence may be further evidence in favour of contraction of leprosy by an infant through skin to skin contact with an infected adult. A. J. R.

SYPHILITIC JUXTA-ARTICULAR NODES. T. Putkonen, H. Teir and K. Pyorala. (1953) *Brit. J. vener. Dis.*, **29**, 71.

Four patients with juxta-articular nodes are reported. All had syphilis previously untreated, three had a node in the region of the great trochanter on both sides, and in two of them this was the only site of occurrence. The histological appearances are described and well illustrated by five photomicrographs. The nodes were observed to regress or disappear in all cases after antisyphilitic therapy. Three patients received only penicillin, while one had both therapeutic malaria and penicillin. The four cases were noted in the course of one year among 95 patients with previously untreated syphilis and, in this series, there were 44 cases of neurosyphilis. The authors conclude that the condition is not so unusual as is generally assumed, and that the apparent association of juxta-articular nodes and neurosyphilis may be merely coincidental. W. G. A.

CLINICAL ASPECTS OF BEJEL. G. W. Csonka. (1953) *Brit. J. vener. Dis.*, **29**, 95.

Some clinical and epidemiological aspects of bejel, a non-venereal treponematosis found amongst the rural Arab population of some Middle-Eastern countries, are described on the basis of 3507 cases seen in Iraq under the auspices of the bejel campaign sponsored by WHO/UNICEF. The relationship of bejel to syphilis and other treponemal diseases is still uncertain, but in practice it responds, like all the others, to penicillin, and this particular antibiotic remains the drug of choice for mass treatment. W. G. A.

"MUTILATING" BEJEL. L. G. G. Jones. (1953) *Brit. J. vener. Dis.*, **29**, 104.

A case is described and well illustrated by three plates. The results of treatment by the single "shot" P.A.M. were dramatic. The routine treatment administered by the WHO/UNICEF Bejel/Syphilis Project in Iraq in different types of bejel is 4 ml. P.A.M. in a single injection (with the exception of those suffering from an osteoperiostitis when the quantity is 8 ml.). Without exception, in all cases treated and followed up, the same clinical response has been noted.
W. G. A.

STEVENS-JOHNSON SYNDROME. E. Friedmann and G. Pathé. (1953) *Ann. Derm. Syph.*, **80**, 132.

Stevens-Johnson syndrome is only a severe form of "polymorphic erythema." The authors discuss at length the various conditions related to this syndrome, with particular reference to the original descriptions by Hebra, Rendu, Baader, Sutton and others, and present two cases of the acute syndrome. They believe that they are essentially the same condition in varying degrees of severity. ACTH has a beneficial effect on the course of the disease. F. F. H.

CLINICAL AND HISTOLOGICAL CRITERIA OF LICHEN PLANUS OF THE SKIN AND MUCOUS MEMBRANES. H. Gougerot and A. Civatte. (1953) *Ann. Derm. Syph.*, **80**, 5.

Gougerot reviews briefly the clinical aspects of lichen planus, including numerous rare forms which he and others have described. Among these are erythemato-squamous types, and invisible forms only recognizable because typical papules have been present previously, or develop subsequently, and forms revealed by pigmentation, etc.; he also describes various lesions appearing on the mucosa which he considers to be lichen planus. Civatte gives a lucid account of the histology of lichen planus. Clinically atypical forms may be histologically typical and vice versa. He believes lichen nitidus is a form of lichen planus but does not accept lichen sclerosus as such; the histological differentiation of lichen planus from "poikilodermie reticulée pigmentaire" may at times be impossible. F. F. H.

PSEUDO LUPUS ERYTHEMATOSUS PROFUNDUS (KAPOSI-IRGANG). L. M. Pautrier. (1953) *Ann. Derm. Syph.*, **80**, 233.

Pautrier has made a special study of L.E. for 50 years but has never seen this condition. He has searched Kaposi's writings and found no clinical reference to such a form, and only a vague histological mention of infiltration in the deeper parts of the dermis. Even a much quoted description by the author's great teacher, Brocq, is shown to have been torn from its context and misinterpreted, whilst the latter never referred in conversation to a deep form. Pautrier reviews several reported cases and shows that they do not fulfil the criteria laid down by Irgang and do not show any involvement of the hypoderm, or else they are confused with other conditions. Possibly Irgang's case may have been a true L.E. of the face associated with hypodermic lesions of Darier-Roussy type, but this rare co-existence does not justify their forming a single disease. The author feels strongly that the myth of L.E. profundus (Kaposi-Irgang) should not be perpetuated. This article should be read in full by anyone presenting a rare condition who has not consulted the original descriptions of it. F. F. H.

PYODERMATITIS VEGETANS OF HALLOPEAU. R. Degos and A. Carteaud. (1953) *Ann. Derm. Syph.*, **80**, 254.

The authors describe a girl of 15 with extensive typical vegetating pustular lesions especially marked over the back and the scalp. Histology showed no signs of pemphigus or dermatitis herpetiformis and culture grew *Staphylococcus aureus*. Remarkable improvement followed injections of strontium bromide, after previous treatments with antibiotics, etc., had failed. The authors feel that this response suggests that nervous influences must play an important part in addition to infection. F. F. H.

HISTOCHEMICAL STUDIES OF HUMAN SKIN. A. Dupré. (1953) *Ann. Derm. Syph.*, **80**, 263.

The author after investigating the nature of the dermo-epidermal junction using MacManus's and other stains concludes that (1) there is a basement membrane which is continuously homogeneous and not fibrillar; (2) chemically it is a lipid-glucoid-protein complex; (3) it arises from the interstitial dermal substance, of which it is only a local physio-chemical modification. It functions partly as a cement and partly as a filter. The article contains some good photomicrographs. F. F. H.

BACTERIOSTATIC AND FUNGISTATIC ACTIVITY OF PROPIONIC AND CAPRYLIC ACIDS AS A FUNCTION OF THEIR pH. A. Georges. (1953) *Arch. belg. Derm. Syph.*, **9**, 1.

Laboratory experiments showed that propionic acid has a greater bacteriostatic effect than caprylic acid, but that caprylic acid has a greater fungistatic effect than propionic acid. The sensitivity of *B. pyocyaneus* to propionic acid and of *C. albicans* to caprylic acid was noteworthy. Both acids lose their activity on neutralization; their action is due, not to their ions, but to their non-dissociated acid molecules. J. K.

USE OF A CYCLOHEXIMIDE MEDIUM FOR ISOLATION OF DERMATOPHYTES FROM CLINICAL MATERIALS. Lucille K. Georg. (1953) *Arch. Derm. Syph., Chicago*, **67**, 355.

The author already uses Sabouraud's medium fortified with penicillin (20 units per ml.) and streptomycin (40 units per ml.) and now adds 0·5 mg. of cycloheximide per ml. This medium, very conveniently, inhibits the growth not only of bacteria but also of saprophytic fungi, and leaves the parasitic fungi a clear field even when obtained from cattle hair. J. K.

THE RELATIVE AND ABSOLUTE VALUE OF SKIN REACTIONS FOR THE DIAGNOSIS OF FOOD ALLERGY. W. Kremer. (1953) *Acta allergol.*, **6**, 124.

Intracutaneous skin tests are important in the diagnosis of food allergy. Elimination of a certain food may lead to increased tolerance or complete disappearance of the hypersensitivity with reversal of a positive test. Repeated eating of a food may result in gradual sensitization. H. T. H. W.

THE EFFECT OF TOPICALLY ADMINISTERED CORTISONE ON EXPERIMENTALLY INDUCED CONTACT DERMATITIS IN HUMAN BEINGS. M. Schwartz. (1953) *Acta allergol.*, **6**, 134.

Cortisone ointment was rubbed for 9 days into the skin of 11 patients previously sensitized to dinitrochlorobenzene. This did not influence the appearance or time relations of a dermatitis subsequently induced, neither did local cortisone treatment affect the course of the dermatitis. H. T. H. W.

HISTAMINE LIBERATORS AND THE INTRADERMAL TUBERCULIN TEST IN HUMAN SUBJECTS. J. Lecomte and Ch. Borensztajn. (1953) *Acta allergol.*, **6**, 89.

The tuberculin reaction is suppressed or reduced by previous local injections of stilbamidine, diaminodecane or cystinamine. This result is probably due to their anti-inflammatory properties rather than their capacity to liberate histamine. H. T. H. W.

ADRENAL CORTICAL HORMONES AND ALLERGIC SKIN DISEASES. Ake Nilzen. (1953) *Acta allergol.*, Suppl. **3**, 13.

Three patients with dermatoses of allergic origin were treated with ACTH or cortisone. In the first eczema became worse, while asthma improved after small doses of ACTH. The second, an exfoliative dermatitis, died of pulmonary tuberculosis which developed during cortisone therapy. The third, a severe angioneurotic oedema following penicillin, responded dramatically to intravenous ACTH. H. T. H. W.

THE ANTI-ALLERGIC ACTION OF COLCHICINE DERIVATIVES. A. Mugler. (1953) *Acta allergol.*, Suppl. **3**, 76.

Colchicine is an effective antipruritic, particularly when given intravenously in doses of 3 mg. or more. Colchicoside is equally effective and much less toxic. It appears to have an ACTH-like action. H. T. H. W.

CLINICAL AND EXPERIMENTAL INVESTIGATIONS ON CUTANEOUS FUNGUS DISEASES IN THE REGION OF HAMBURG, 1948-1950. H. Gotz. (1952) *Arch. Derm. Syph., Berl.*, **195**, 1.

A statistical survey showing that the troublesome *Trichophyton rubrum* (for which the name *Epidermophyton rubrum* Castellani is preferred, as it usually does not invade hair) is increasing in incidence round Hamburg. M. F.

CONCERNING THE SPECIES SCOPULARIOPSIS. H. D. Jung. (1952) *Arch. Derm. Syph., Berl.*, **195**, 77.

A gummatous swelling over the thyroid caused by *Scopulariopsis brevicaulis* (Sacc.) Bain var. *hominis* Brumpt et Langeron, obtained in pure culture. A clinical diagnosis is not easy, individual host reaction is various. M. F.

CONCERNING IODINE SENSITIVITY IN DERMATITIS HERPETIFORMIS. H. W. Spier, C. G. Schirren, U. Dessin and T. Ewinger. (1952) *Arch. Derm. Syph., Berl.*, **195**, 105.

The potassium iodide patch test is non-specific and hence not diagnostic. The clinical fact that attacks of dermatitis herpetiformis may be provoked by ingestion of small quantities of potassium iodide is not proof of iodine allergy. M. F.

SIGNIFICANCE OF PAPER ELECTROPHORESIS IN DERMATOLOGY. C. F. Funk, W. Grassmann, H. Walther and K. Hannig. (1952) *Arch. Derm. Syph., Berl.*, **195**, 208.

The ready determination of the values of serum proteins helps in the consideration of various dermatoses. M. F.

STERNAL MARROW PUNCTURE FINDINGS AND RELATION TO BLOOD SEDIMENTATION RATE IN ACRODERMATITIS CHRONICA ATROPHICANS. W. Hauser. (1952) *Arch. Derm. Syph., Berl.*, **195**, 164.

Twenty-five patients were examined. Lymphocytes, plasma cells, mast cells and eosinophils were increased. M. F.

OBSERVATIONS ON CHEMOTHERAPY OF MYCOTIC DISEASES. R. Richter and W. Temps. (1952) *Arch. Derm. Syph., Berl.*, **195**, 138.

2·2′-dioxy-5·5′ dichlorodiphenylsulphide (D-25, Novex) was tested by local and internal administration on 66 patients with various fungous diseases. There were no toxic symptoms as far as liver function, blood picture and urine analysis were concerned. Oral administration caused diarrhoea in 20% of patients and in one treatment had to be stopped. The results—50 cured, 16 improved. Systemic mycoses were likewise benefited. M. F.

THE TREATMENT OF ERYTHEMATODES CHRONICUS DISCOIDES WITH RUTIN. C. Serowy. (1953) *Derm. Wschr.*, **127**, 590.

Most of the author's 32 patients were landworkers. Rutin 1 g. was given 5–7 times daily. The first sign of improvement appeared as a rule after 25 days: 10 of the 32 patients became well in an average of 137 days, 2 relapsing 6 months later: 11 patients became worse. The most noticeable beneficial effect was on the hyperkeratosis, even old very horny patches yielding (this is illustrated photographically). He considers that rutin acts by inhibiting the action of hyaluronidase, the heightened permeability of vessels and fluid exudation, etc., and following normalization of the vascular system, on the hyperkeratosis, by increasing oxidation. Light sensitivity was decreased by rutin. M. S. S.

SKEIN-LIKE FORMS OF SUPERFICIAL PHLEBITIS. O. Braun-Falco. (1953) *Derm. Wschr.*, **127**, 506.

The author discusses two main types of this unusual complaint, phlébite fil de fer (Favre), with predilection for the limbs, usually the lower, and thrombo-phlébites et périphlébites de la paroi thoracique (Mondor's disease)—until now thought always to be unilateral. He notes the frequent history of antecedent trauma, often operative, and co-existence of infection, e.g., tuberculosis; the fact that it affects predominantly females (75%) between the ages of 25 and 55; also the virtual absence of signs or symptoms beyond the metallic hardness felt on palpation. His own patient, a man aged 43, was an unusual example: both types of the disease were present, and in the course of 8 months appeared bilaterally to involve both sides of the anterior chest wall, and both axillae extending in parallel strands (the thickness of spaghetti) to involve the elbow flexures; in strands softer than usual the dorsum of the penis (not previously described and here accompanied by oedema) and one strand in the mid-line of the neck. One arm and hand were oedematous. Chronic tonsillitis and earlier resection of a gastric carcinoma. Spontaneous almost entire involution of some of the lesions after 4 months. The histology of a lesion several days old from the upper arm was that of a beginning phlebitis ? thrombosing; and a lesion 6 weeks old from the chest wall showed obliteration of the vessel structure (with only a few remains of the media), and recanalization; at first sight longitudinally it resembled a nerve rather than a vessel. M. S. S.

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